METHOD AND COMPOSITIONS FOR IDENTIFYING ANTI-HIV THERAPEUTIC COMPOUNDS

This non-provisional application is a continuation-in-part of U.S. Non-provisional Application No. 10/424,186, filed April 25, 2003, which claims the benefit of U.S. Provisional Application No. 60/375,622, filed April 26, 2002, U.S. Provisional Application No. 60/375,779, filed April 26, 2002, U.S. Provisional Application No. 60/375,834, filed April 26, 2002, and U.S. Provisional Application No. 60/375,665, filed April 26, 2002, all of which are incorporated herein by reference in their entirety.

This application is also a continuation-in-part of U.S. Non-provisional Application No. 10/423,496, filed April 25, 2003, which claims the benefit of U.S. Provisional Application No. 60/375,622, filed April 26, 2002, U.S. Provisional Application No. 60/375,779, filed April 26, 2002, U.S. Provisional Application No. 60/375,834, filed April 26, 2002, and U.S. Provisional Application No. 60/375,665, filed April 26, 2002, all of which are incorporated herein by reference in their entirety.

This application is also a continuation-in-part of U.S. Non-provisional Application No. 10/424,130, filed April 25, 2003, which claims the benefit of U.S. Provisional Application No. 60/375,622, filed April 26, 2002, U.S. Provisional Application No. 60/375,779, filed April 26, 2002, U.S. Provisional Application No. 60/375,834, filed April 26, 2002, and U.S. Provisional Application No. 60/375,665, filed April 26, 2002, all of which are incorporated herein by reference in their entirety.

This application is also a continuation-in-part of International Application No. PCT/US03/12901, filed April 25, 2003, PCT/US03/12926, filed April 25, 2003, and PCT/US03/12943, filed April 25, 2003, all of which applications are incorporated herein by reference in their entirety.

This application also claims the benefit under §119(e) of U.S. Provisional Application No. 60/465,810, filed April 25, 2003, U.S. Provisional Application No. 60/465,721, filed April 25, 2003, and U.S. Provisional Application No. 60/465,824, filed April 25, 2003, all of which applications are herein incorporated by reference in their entirety.

Field of the Invention

The invention relates generally to methods and compositions for identifying compounds having therapeutic activity against human immunodeficiency virus (HIV).

Background of the Invention

Anti-HIV compounds are well established and have achieved significant therapeutic benefit. However, existing therapeutics remain less than optimal. Conspiring to reduce patient compliance and therapeutic efficacy are toxicity, resistant HIV, poor bioavailability, low potency, and frequent and inconvenient dosing schedules, among other failings. The need to administer very large tablets and requirements for frequent dosing characterize a number of important anti-HIV therapeutics, most particularly the HIV protease inhibitors. While significant advances have been made in preparing improved nucleotide analogue anti-HIV therapeutics (see WO 02/08241, EP 820,461 and WO 95/07920, all of which are hereby incorporated by reference), other anti-HIV therapeutic drug classes remain encumbered with severe deficiencies.

Summary of the Invention

The present invention provides methods and compositions for identifying therapeutic anti-HIV compounds having improved pharmacological and therapeutic properties. In particular, this invention provides for novel candidate therapeutic anti-HIV compounds and methods for screening them to identify compounds having such beneficial properties.

In accordance with this invention, a method is provided that comprises (a) identifying a non-nucleotide prototype compound; (b) substituting the prototype compound with an esterified carboxyl or esterified phosphonate-containing group to produce a candidate compound; and (c) determining the anti-HIV activity of the candidate compound.

In another embodiment, a method is provided that comprises (a) selecting a non-nucleotide candidate compound containing at least one esterified carboxyl or esterified phosphonate-containing group and (b) determining the intracellular persistence of the candidate compound or a esterolytic metabolite of the esterified carboxyl or phosphonate-containing group thereof.

In a further embodiment, determining the anti-HIV activity of the candidate compound comprises determining the anti-HIV activity of a carboxylic acid or phosphonic acid-containing metabolite of the candidate compound, which carboxyl acid or phosphonic acid-containing

metabolite is produced by esterolytic metabolic cleavage of the esterified carboxyl or phosphonate-containing group. In another embodiment determining anti-HIV activity comprises determining the the tissue selectivity and/or the intracellular residence time of at least one of said intracellular carboxylic acid or phosphonic acid-containing metabolites.

In another embodiment of this invention, a library of anti-HIV candidate compounds is provided that comprises at least one non-nucleotide prototype compound substituted by an esterified carboxyl or phosphonate group. Such libraries facilitate large-scale screening of candidate compounds.

This invention is an improvement in the conventional methods for identifying therapeutic anti-HIV compounds. Thus, in a method for identifying an anti-HIV therapeutic compound, the improvement comprises substituting a prototype compound with an esterified carboxyl or phosphonate and assaying the resulting candidate compound for its anti-HIV activity.

Adding the esterified carboxyl or phosphonate group to the prototype molecule produces significant advantages in the pharmacologic properties of the prototype. Without being held to any particular method of operation of the invention, it is believed that the ester(s) mask the charge of the carboxyl or phosphonate and permit the candidate to enter HIV infected cells, in particular peripheral blood mononuclear cells (PBMCs). Once the candidate has entered the cells it is processed by biological mechanisms (most notably, it is believed, by a newly discovered PBMC enzyme which we designate GS-7340 Ester Hydrolase) to produce at least one metabolite containing a free carboxylic acid and/or phosphonic acid. This metabolite is antivirally active against HIV. These charged metabolic depot forms are exceptionally persistent in the cells, thereby permitting substantial reductions in the frequency of dosing compared to the parental prototype, among other advantages. In addition, the esterified carboxyl or phosphonate substituent may direct the selective distribution of the prototype to tissues (most particularly lymphoid tissues such as PBMCs) which are noted sites of HIV infection, thereby potentially reducing systemic dose and toxicity.

In further embodiments, assaying for anti-HIV activity optionally comprises screening the candidate compounds for their susceptibility to esterolytic cleavage by isolated GS-7340 Ester Hydrolase. The isolated Hydrolase is a further embodiment of this invention.

Since GS-7340 Ester Hydrolase may interact with other compounds than the anti-HIV candidates, it will be of pharmacologic utility to determine if the enzyme is cleaving such other

compounds. Thus, another embodiment of this invention is a method comprising obtaining a substantially pure organic molecule, optionally contacting the organic molecule with another molecule to produce a composition, contacting GS-7340 Ester Hydrolase with said organic molecule or composition, and optionally determining whether the organic molecule has been cleaved by the Hydrolase.

In another embodiment, a method is provided comprising contacting GS-7340 Ester Hydrolase with an organic compound in a cell-free environment.

In a further embodiment, a method is provided comprising contacting GS-7340 Ester Hydrolase with an organic compound in an *in vitro* or cell culture environment.

In another embodiment, a composition is provided comprising a substantially pure organic compound and isolated GS-7340 Ester Hydrolase.

In another embodiment, a composition is provided comprising an organic compound and GS-7340 Ester Hydrolase in an *in vitro* or cell culture environment.

These and other embodiments of this invention are more fully described in the following disclosure.

Detailed Description of the Invention

The following disclosure contains detailed embodiments of the practice of the invention. These are provided to more fully describe the invention, but the invention is not limited to these embodiments.

"Anti-HIV activity" of candidates is determined by any method for assaying the HIV inhibitory activity of a substance. Many such methods are well known, and range from *in vitro* enzyme assays (*e.g.*, HIV reverse transcriptase or integrase assays) to animal studies (*e.g.*, SIV in chimps) and human clinical trials. Included with this term are any assays bearing on the therapeutic anti-HIV efficacy of a substance, *e.g.*, HIV resistance determinations, biodistribution, and intracellular persistence.

"Candidate compound" is an organic compound containing an esterified carboxylate or phosphonate. Optionally, candidate compounds excluded compounds heretofore known to have anti-HIV activity. With respect to the United States, the candidate compounds herein exclude compounds that are anticipated under 35 USC §102 or obvious under 35 USC §103 over the prior art. In other jurisdictions using the novelty and inventive step criteria, the candidate compounds exclude compounds not novel or which lack inventive step over the prior art.

However, libraries containing candidate compounds optionally comprise known compounds. These may be, for example, reference compounds having known anti-HIV activity.

"Non-nucleotide" means any compound that has all of the following characteristics: It does not already contain an esterified carboxyl or phosphonate, it is not a phosphonate or phosphate-containing compound disclosed in WO 02/08241, EP 820,461 or WO 95/07920 and it does not already contain a phosphonate group. GS-7340 is an example of a nucleotide anti-HIV compound. Many other examples of such compounds are known. These compounds are excluded from the scope of prototype compounds and are not employed in the candidate compound screening method or candidate compound ompositions of this invention. For the most part, the nucleotide analogues comprise the substructure $-OC(H)_2P(O)=$ coupled (usually at the 9 position of purine bases or the 1 position of pyrimidine bases) via a sugar or cyclic or acyclic sugar analogue (aglycon) to a nucleotide base or an analogue thereof. The base analogues typically are substituted, usually at extracyclic N atoms, or are the aza or deaza analogues of the naturally occuring base scaffolds. They are fully set forth in the above described art and are well known in the field. See for example U.S. Patent 5,641,763 and related patents and publications by Antonin Holy.

Optionally excluded from the scope of the libraries of this invention are any phosphonates disclosed by WO99/33815, WO99/33792, WO99/33793, WO00/76961 and their related, progeny and parental filings, all of which are hereby incorporated by reference. However, unless expressly excluded by the claims herein, such compounds shall be considered candidate compounds. Further, the act of making and screening the phosphonates of such filings to determine their intracellular persistence (whether by preclinical assays such as that using GS-7340 Ester Hydrolase, or by clinical studies) falls within the scope hereof, as does obtaining regulatory approval to market one of them and selling the selected phosphonate.

"Non-nucleoside" means any compound that is not a nucleotide base linked to a sugar or aglycon (cyclic or acyclic) and terminating at the 5' position (or the analogous position in nucleosides containing sugar analogues) by hydroxyl or a group which is metabolized *in vivo* to hydroxyl. The nucleosides are distinguishable from the nucleotides in not containing a phosphate or, in the case of relevant nucleotide analogues, a phosphonate.

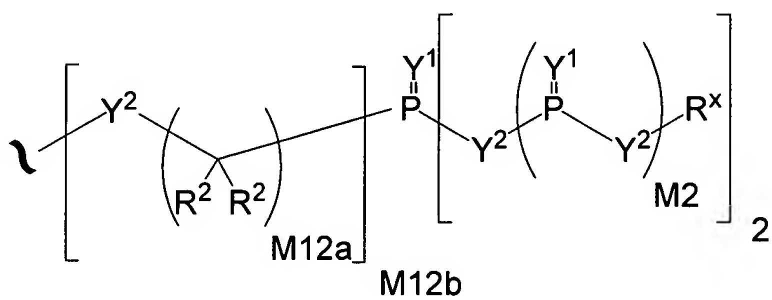
"Phosphonate-containing group" is a group comprising a phosphorus atom singly bonded to carbon, double bonded to oxygen and singly bonded to two other groups through oxygen,

sulfur, or nitrogen. In general, the carbon bond is to a carbon atom of the prototype or a linking group to the prototype and the single bonds to oxygen, nitrogen or sulfur are bonds to oxy or thioesters or are amino acid amidates in which the terminal carboxyl group(s) are esterified.

"Carboxyl-containing groups" are any group having a free carboxyl serving as the site for esterification. An "organic acid" is any compound containing carboxyl and at least one additional carbon atom.

The "esterified carboxyl or esterified phosphonate group" is any group capable of intracellular processing to yield a free carboxyl and/or free phosphonic acid. The structure of these groups is not important other than that the free acid be produced intracellularly. Preferably, systemic or digestive esterolysis is minimized in preference to intracellular hydrolysis. This permits maximum migration of the candidate into target cells and maximum intracellular retention of the acid metabolites.

Suitable exemplary esterified carboxyl or phosphonate groups are described herein. Others are identified by screening for esterolysis *in vivo*, in PBMCs or using GS-7340 Ester Hydrolase. These groups have the structure A^3, wherein A^3 is a group of the formula

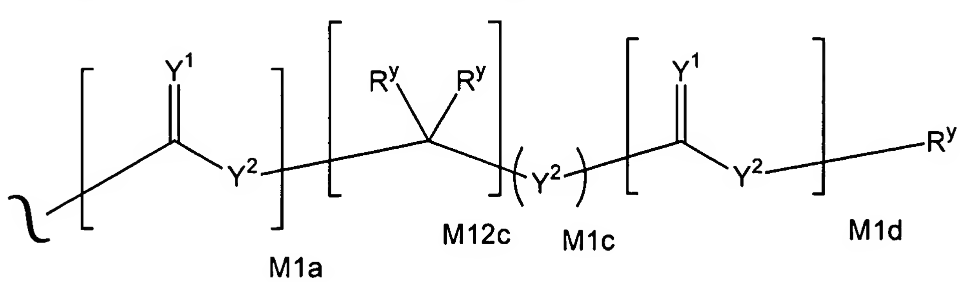


in which:

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, -$S(O)_{M2}$-, or -$S(O)_{M2}$-$S(O)_{M2}$-;

R^x is independently H, R^1, W^3, a protecting group, or a group of the formula:



;

R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^1, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

R^{5a} is independently alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2-18 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M1a, M1c, and M1d are independently 0 or 1; and

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

The esterified group is attached to the prototype through a bond or via intermediary linking groups such as the A^1 subgroup $-[Y^2-(C(R^2)_2)_{m12a}]_{m12b}Y^2W^6-$ defined below.

Candidates optionally are substituted with a single substituent which contains both an esterified carboxyl and an esterified phosphonate. In addition, or as an alternative, the candidate contains separate substituents bearing esterified carboxyl and/or phosphonate groups. An example of a combined group would a phosphonate in which a free valence of the phosphorus atom is bonded to the hydroxy of an hydroxyorganic acid or to the amino group of an amino acid wherein the carboxyl groups of the organic acid or amino acid are esterifed.

"Esterified" means that the phosphonate or carboxyl is bonded to a carbon atom-containing group through oxygen or sulfur, as in –P(O)(OR)- or –COOR for example, where R is a carbon containing group such as alkyl or aryl.

"Protecting group" is a group covalently bonded to a labile site on the candidate compound, which site is expected to be labile under the conditions to be encountered by the candidate, for example during synthetic procedures, during exposure to ambient conditions, and the conditions found in *in vivo* environments. The protecting group serves to prevent degradation or otherwise undesired conversions at the labile site. Extensive disclosure of various exemplary protecting groups is found *infra.*

"Intracellular depot metabolite" is an esterolytic metabolite of the esterified carboxyl or phosphonate whereby a charged carboxyl or phosphonic acid is revealed. An example is Metabolite X, further described in the examples.

"Tissue selectivity" of candidate compounds is determined by procedures set forth in WO02/08241. The object of this determination is to find whether or not the candidate (and by extension its depot forms) are enriched in one tissue or another. It is expected that compounds containing the carboxyl or phosphonate groups as described herein will be preferentially enriched in lymphoid tissue such as PBMCs.

"Intracellular residence time," "intracellular persistence," "intracellular half life" and the like refers to a measure of the time that a candidate molecule or its anti-HIV active metabolite is found within a given cell after introduction of the esterified candidate into the cell. Any technique is suitable that demonstrates how long a candidate or its anti-HIV active metabolite(s) remain in a cell. Further description of suitable assay procedures are set forth *infra*. Ideally, the method for measuring residence time will measure the retention time of the metabolite at a concentration adequate to inhibit HIV.

A "prototype compound" is any organic compound. In general, in the method of this invention one will select prototype compounds having known structures and synthesis routes in order to reduce the synthetic burden and development costs. Typically, the prototype compound will be one that has, or at least is suspected, to have anti-HIV activity. However, since the prototype compound is serving only as a starting point for preparing candidate compounds to be screened, it is not essential that it have, or be known or suspected to have, preexisting anti-HIV activity. The prototype compound need not be published or known generally to the public. In fact, the method of this invention is advantageously practiced in on-going proprietary research programs where anti-HIV compounds are continually identified and optimized. It also should be understood that identification or selection of the prototype compound need not be temporally related to that of the candidate compound. This means that the prototype might be identified after one or more related candidate compounds are made, or the prototype might be an early version of a compound class that has advanced further into development before the candidate based on the early prototype is actually synthesized. The prototype compound also may be entirely conceptual or may be in various phases of development. No actual prototype need have been made, nor tested for activity or any other properties. This is often the case with candidates that are the product of truncating an existing compound and then inserting a linker group in place of all or a part of the omitted portion. In addition, it is not necessary that the prototype compound be conceived independently of the esterified substituent, *i.e.*, it is not necessary to have the prototype in mind before designing the esterified substitution. The conception of the candidate compound optionally is a single act. Of course, the candidate compound may be based on a prototype which is in fact a previously made candidate compound and the subsequent candidate is multiply substituted with the carboxyl or phosphonate ester. Also, it will be understood that a candidate or group of candidates compounds optionally are based on an original prototype even though intervening candidates or libraries of candidates have been made.

The prototypes generally serve as the starting point for designing and identifying candidate compounds. Generally a prototype will not contain a phosphonate or carboxyl group, but it may do so if the phosphonate or carboxyl are not esterified (since candidates contain esterified phosphonate or carboxyl groups). It is most efficient to start with prototypes already known to have anti-HIV activity (preferably compounds active against anti-HIV protease, HIV integrase or HIV polymerase), but it is not essential to do so. For example, a prototype

optionally is a subsegment or fragment of a compound known to possess anti-HIV activity, even though the fragment need not be active against HIV in its own right. In this instance, the phosphonate or carboxyl group restores anti-HIV activity to the candidate.

"Linker" or "link" is a bond or an assembly of atoms binding the prototype to the esterified phosphonate or carboxyl-containing group. The nature of the linker is not critical. The linker need not be involved in the interactions of the esterified carboxyl or phosphonate group with GS-7340 Ester Hydrolase or other processing enzymes, nor need it be involved in the therapeutic interaction of the prototype with its target protein. This is not to say that these functions could not be enhanced or influenced by the linker, but it is not necessary that the linker perform or contribute to such functions. Thus, it is a straight-forward matter of elemental organic chemistry to devise suitable linkergroups and methods for joining the esterified groups.

Some general principles are useful in selecting suitable linkergroups, despite their lack of criticality. First, they will not be so bulky as to interfere with the interaction of the remainder of the prototype with its target protein, *e.g.*, HIV protease inhibitor, nor will they bear reactive or unstable groups once the linkage has been accomplished. Such chemically reactive groups will be well known to the artisan, and the parameters of bulky linkers can be evaluated by molecular modeling. Resources are available to model proteins involved in a number of diseases and disorders of lymphoid tissues, in particular HIV protease. In general, the linker will be relatively small, on the order of about 16-500 MW, typically about 16-250, ordinarily about 16-200, although as noted the linker can be as small as a bond. It generally will be substantially linear, containing less than about 40% of the total MW of the linkeratoms being found in branching groups, typically less than 30% and ordinarily less than about 20%.

The backbone of such linkergroups ideally will not contain any atom that is known to be labile to cleavage by biological processes or otherwise subject to hydrolysis in biological fluids. Typical suspect groups would be esters or amides in the backbone of the linker. The object is for the carboxyl or phosphonate to survive intracellular processing, with only the ester(s) being hydrolyzed, and the presence of labile groups in the backbone would jeopardize this function. However, if enzymatic access to labile atoms or groups is sterically hindered, *e.g.*, by a cycloalkyl group or branched alkyl group, then labile sites optionally may be used in the linker. Labile groups also optionally are can be found in locations other than backbone positions, *e.g.*, on branching groups or cyclic substituents, where their potential cleavage would not result in the

loss of the free acid functionality. Backbone alkyls, alkyl ethers (S or O), or alkyl containing N in any oxidation state are usually satisfactory. Generally the linker backbone is linear rather than branched or cyclic (although it may be desired to use branching or cyclic backbones when multiple esterified groups are substituted onto the prototype). The linker generally is chosen to permit substantial rotational freedom to the esterified group, and for this reason backbone double or triple bonds are not favored unless it is expected that they would be metabolized to less rotationally confined structures *in vivo* (*e.g.*, oxidized to hydroxyl substituents). If it is desired to avoid interactions with the target protein then the linker optimally will have neither highly charged nor strongly hydrophobic character, although as noted such properties can have advantages in enhancing anti-HIV activity.

The typical linker to phosphonate will comprise at least the group $-OCH_2-$ (wherein the carbon is linked to the phosphorous atom), but many others will be apparent to the artisan or are described elsewhere herein.

Synthetic ease optionally will play a role in selection of the linker. For this reason, many linkers will contain a backbone or chain heteroatom such as 1 to 3 S, N or O. However, occasionally the prototype compound will contain a convenient site for insertion of the linker, *e.g.*, a pendant hydroxyl, thus enabling a small linkergroup because the phosphorous atom can be linked directly, or virtually directly, to the prototype. Synthetic routes also can be devised readily that permit direct linkage of the phosphorous atom to the prototype, in which case the linker is merely a bond.

The linker optionally is grafted onto the prototype, or the prototype compound is optionally is modified to remove group(s) which then are replaced with linker(s). This may facilitate the synthesis of the candidate compound or, in some instances, may fortuitously improve the properties of the candidate. This may or may not be more efficient that simply grafting A^3 onto the prototype.

Typically, the starting point in devising a facile synthetic route for a candidate compound is to analyze the synthons employed in known methods for preparing the remainder of the prototype compound, concentrating on synthons which could contribute at least a part of the esterified group. Such synthons optionally are modified to contain the esterified group or a portion thereof (*e.g.*, the acid, which is then esterified in a later step). They are then introduced into the remainder of the candidate in substantially the same fashion as the prototype or

antecedent compound. Alternatively, a reactive group is introduced into the synthon before it is assembled into the precursor, and it is this group that is reacted with an intermediate for the carboxyl or phosphonate group. If necessary, suitable protecting groups are employed to facilitate the synthesis.

The site for insertion of the esterified carboxyl or phosphonate group on the prototype will vary widely. The esterified group preferably is substituted at any location on the prototype that does not bind substantially with the target protein or affect the functioning of a group that does interact with the target protein. These sites are identified by molecular modeling, by consulting systematic SAR studies or by preparing pilot candidate compounds. However, it is also within the scope of this invention to insert the esterified groups at a site which is involved in binding the prototype to the target protein. Such sites optionally are used if (a) the linker reasonably replicates the function of the group on the prototype that it is displacing, *e.g.*, it possesses a side chain containing the group, (b) if the loss in binding affinity is not critical to the functioning of the prototype or (c) if other substitutents are introduced into the prototype that compensate for any loss in activity caused by the insertion of the linker.

The linker generally will contain at least two free valences (1 for the prototype and 1-3 for the esterified groups). Multivalent linkergroups can be employed to form a cyclic structure, being joined at 2 or more sites on the prototype and forming a bridge, the bridge in turn being subsituted with one or more esterified carboxyl or phosphonate groups or including at least one atom encompassed within such groups. In addition, the linker does not need to be bound to the esterified group and/or the remainder of the prototype by a covalent bond, nor need it consist solely of covalently bonded atoms. Any bond meeting the basic criteria herein will be satisfactory, as for example linkage by chelation or other stable non-covalent attachment systems are included within the scope of the term "bond" as used herein.

Linkers also include polymers, *e.g.*, those containing repeating units of alkyloxy (*e.g.*, polyethylenoxy, PEG, polymethyleneoxy) and/or alkylamino (*e.g.*, polyethyleneamino, Jeffamine™). Other linker groups include diacid ester and amides including succinate, succinamide, diglycolate, malonate, and caproamide.

Suitable linker groups optionally are prescreened by testing model candidates in the same fashion set forth herein for disclosed candidate compounds, *e.g.*, screening using the Ester

Hydrolase described herein, or by studying the effect of a model linker-containing candidate compound in PBMCs.

Typical linkers have the A^1 substructure $-[Y^2-(C(R^2)_2)_{m12a}]_{m12b}Y^2W^6-$wherein Y^2, R^2, m12a and m12b are defined elsewhere herein, W^6 is W^3 having from 1 to 3 free valences and the prototype is bound to the Y^2 with free valence. However, many other structures would be apparent to the ordinary artisan and can be prepared by conventional means using the guidance herein.

Defined Chemical Terms

"Alkyl" is C_1-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. Examples are methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $-CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $-C(CH_3)_3$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$)), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$.

"Alkenyl" is C_2-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, *i.e.* a carbon-carbon, sp^2 double bond. Examples include, but are not limited to: ethylene or vinyl ($-CH=CH_2$), allyl ($-CH_2CH=CH_2$), cyclopentenyl ($-C_5H_7$), and 5-hexenyl ($-CH_2\ CH_2CH_2CH_2CH=CH_2$).

"Alkynyl" is C_2-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, *i.e.* a carbon-carbon, *sp* triple bond. Examples include, but are not limited to: acetylenic ($-C\equiv CH$) and propargyl ($-CH_2C\equiv CH$).

"Alkylene" refers to a saturated, branched or straight chain or cyclic hydrocarbon radical of 1-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. Typical alkylene radicals include, but are not limited to: methylene ($-CH_2-$) 1,2-ethyl ($-CH_2CH_2-$), 1,3-propyl ($-CH_2CH_2CH_2-$), 1,4-butyl ($-CH_2CH_2CH_2CH_2-$), and the like.

"Alkenylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. Typical alkenylene radicals include, but are not limited to: 1,2-ethylene (-CH=CH-).

"Alkynylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkyne. Typical alkynylene radicals include, but are not limited to: acetylene (-C≡C-), propargyl ($-CH_2C{\equiv}C-$), and 4-pentynyl ($-CH_2CH_2CH_2C{\equiv}CH-$).

"Aryl" means a monovalent aromatic hydrocarbon radical of 6-20 carbon atoms derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Typical aryl groups include, but are not limited to, radicals derived from benzene, substituted benzene, naphthalene, anthracene, biphenyl, and the like.

"Arylalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, 2-phenylethen-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, 2-naphthylethen-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. The arylalkyl group comprises 6 to 20 carbon atoms, *e.g.*, the alkyl moiety, including alkanyl, alkenyl or alkynyl groups, of the arylalkyl group is 1 to 6 carbon atoms and the aryl moiety is 5 to 14 carbon atoms.

"Substituted alkyl", "substituted aryl", and "substituted arylalkyl" mean alkyl, aryl, and arylalkyl respectively, in which one or more hydrogen atoms are each independently replaced with a substituent. Typical substituents include, but are not limited to, -X, -R, $-O^-$, -OR, -SR, $-S^-$, $-NR_2$, $-NR_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, NC(=O)R, -C(=O)R, -C(=O)NRR $-S(=O)_2O^-$, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, -OP(=O)O_2RR, -P(=O)O_2RR -P(=O)$(O^-)_2$, -P(=O)$(OH)_2$, -C(=O)R, -C(=O)X, -C(S)R, -C(O)OR,

-C(O)O⁻, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, -C(NR)NRR, where each X is independently a halogen: F, Cl, Br, or I; and each R is independently -H, alkyl, aryl, heterocycle, protecting group or prodrug moiety. Alkylene, alkenylene, and alkynylene groups may also be similarly substituted.

"Heterocycle" as used herein includes by way of example and not limitation these heterocycles described in Paquette, Leo A. Principles of Modern Heterocyclic Chemistry (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; The Chemistry of Heterocyclic Compounds, A Series of Monographs (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* (1960) 82:5566.

Examples of heterocycles include by way of example and not limitation pyridyl, dihydroypyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazoly, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, and isatinoyl.

By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles

include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

By way of example and not limitation, nitrogen bonded heterocycles are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetedyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

"Carbocycle" means a saturated, unsaturated or aromatic ring having 3 to 7 carbon atoms as a monocycle or 7 to 12 carbon atoms as a bicycle. Monocyclic carbocycles have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to 12 ring atoms, *e.g.*, arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system. Examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, phenyl, spiryl and naphthyl.

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, *e.g.*, melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., <u>McGraw-Hill Dictionary of Chemical Terms</u> (1984) McGraw-Hill Book Company, New

York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York. Many organic compounds exist in optically active forms, *i.e.*, they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D andthe linkeror R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d andthe linkeror (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or 1 meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

Recursive Substituents

Selected substituents within the compounds of the invention are present to a recursive degree. In this context, "recursive substituent" means that a substituent may recite another instance of itself. Because of the recursive nature of such substituents, theoretically, a large number of compounds may be present in any given embodiment. For example, R^x contains a R^y substituent. R^y can be R^2, which in turn can be R^3. If R^3 is selected to be R^{3c}, then a second instance of R^x can be selected. One of ordinary skill in the art of medicinal chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties include, by of example and not limitation, physical properties such as molecular weight, solubility or log P, application properties such as activity against the intended target, and practical properties such as ease of synthesis.

By way of example and not limitation, W^3, R^y and R^3 are all recursive substituents in certain embodiments. Typically, each of these may independently occur 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0, times in a given embodiment. More typically, each of these may independently occur 12 or fewer times in a given embodiment. More typically yet, W^3 will occur 0 to 8 times, R^y will occur 0 to 6 times and R^3 will occur 0 to 10 times in a

given embodiment. Even more typically, W^3 will occur 0 to 6 times, R^y will occur 0 to 4 times and R^3 will occur 0 to 8 times in a given embodiment.

Recursive substituents are an intended aspect of the invention. One of ordinary skill in the art of medicinal chemistry understands the versatility of such substituents. To the degree that recursive substituents are present in an embodiment of the invention, the total number will be determined as set forth above.

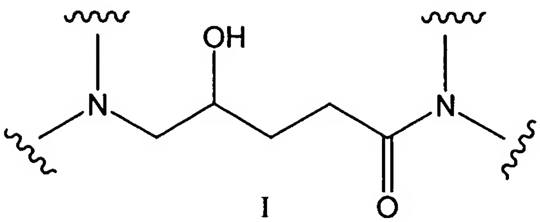
HIV Protease Inhibitor Compounds

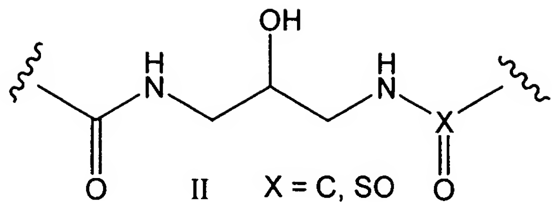
The compounds of the invention include those with HIV protease inhibitory activity. In particular, the compounds include HIV protease inhibitors. The compounds of the inventions bear a phosphonate group, which may be a prodrug moiety.

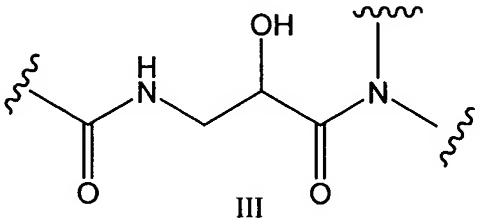
In various embodiments of the invention one identifies compounds that may fall within the generic scope of the documents cited under the definition of the terms ILPPI (Indinavir-like phosphonate protease inhibitors, Formula I); AMLPPI (Amprenavir-like phosphonate protease inhibitors, Formula II); KNILPPI (KNI-like phosphonate protease inhibitors, Formula III); RLPPI (Ritonavir-like phosphonate protease inhibitors, Formula IV); LLPPI (Lopinavir-like phosphonate protease inhibitors, Formula IV); NLPPI (Nelfinavir-like phosphonate protease inhibitors, Formula V); SLPPI (Saquinavir-like phosphonate protease inhibitors, Formula V); ATLPPI (Atanzavir-like phosphonate protease inhibitors, Formula VI); TLPPI (Tipranavir-like phosphonate protease inhibitors, Formula VII); and CCLPPI (Cyclic carbonyl-like phosphonate protease inhibitors, Formula VIIIa-d) all of which comprise a phosphonate group, *e.g.*, a phosphonate diester, phosphonamidate-ester prodrug, or a phosphondiamidate-ester (Jiang *et al.*, US 2002/0173490 A1).

Whenever a compound described herein is substituted with more than one of the same designated group, *e.g.*, "R^1" or "R^{6a}", then it will be understood that the groups may be the same or different, *i.e.*, each group is independently selected. Wavy lines indicate the site of covalent bond attachments to the adjoining groups, moieties, or atoms.

Compounds of the invention are set forth in the schemes, examples, descriptions and claims below and include the invention includes compounds having Formulas I, II, III, IV, V, VI, VII and VIIIa-d:


I


II X = C, SO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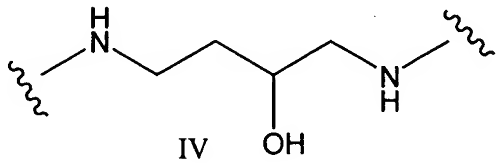
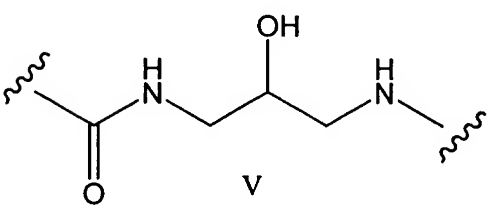
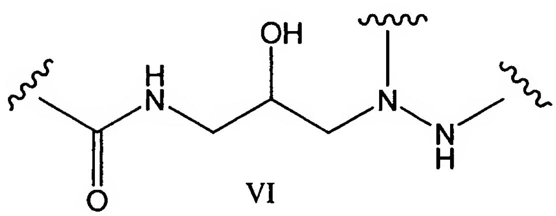

IV


V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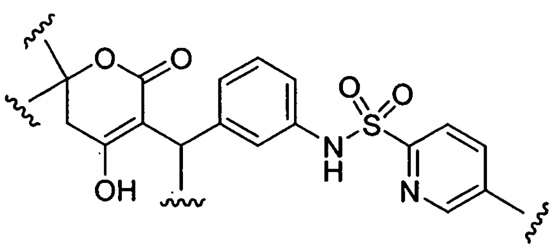
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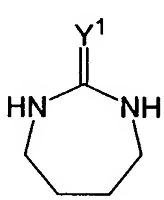
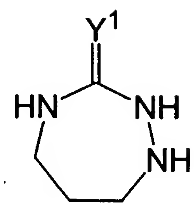
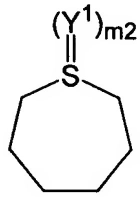
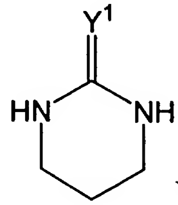

VIIIa


VIIIb


VIIIc and


VIIId;

where a wavy line indicates the other structural moieties of the compounds.

Formula I compounds have a 3-hydroxy-5-amino-pentamide core. Formula II compounds have a 2-hydroxy-1, 3-amino-propylamide or 2-hydroxy-1,3-amino-propylaminosulfone core. Formula III compounds have a 2-hydroxy-3-amino-propylamide core. Formula IV compounds have a 2-hydroxy-4-amino-butylamine core. Formula V compounds have a acylated 1,3-diaminopropane core. Formula VI compounds have a 2-hydroxy-3-diaza-propylamide core. Formula VII compounds have a sulfonamide 5,6-dihydro-4-hydroxy-2-pyrone core. Formula VIIIa-d compounds have a six or seven-membered ring, and a cyclic carbonyl, sulfhydryl, sulfoxide or sulfone core, where Y^1 is oxygen, sulfur, or substituted nitrogen and m2 is 0, 1 or 2.

Formulas I, II, III, IV, V, VI, VII and VIIIa-d are substituted with one or more covalently attached groups, including at least one phosphonate group. Formulas I, II, III, IV, V, VI, VII and VIIIa-d are substituted with one or more covalently attached A^0 groups, including simultaneous substitutions at any or all A^0. A^0 is A^1, A^2 or W^3. Compounds of Formulas I, II, III, IV, V, VI, VII and VIIIa-d include at least one A^1.

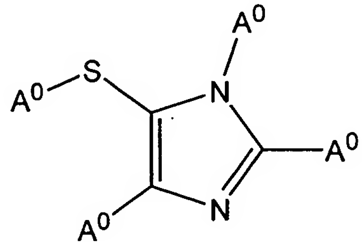
Non-Nucleotide Reverse Transcriptase Inhibitor (NNRTI) Compounds

The compounds of the invention include those with anti-HIV activity. In particular, the compounds include non-nucleotide reverse transcriptase inhibitors (NNRTI). The compounds of the inventions bear a phosphonate group, which may be a prodrug moiety.

In one embodiment of the invention, one identifies compounds that may fall within the generic scope of the documents cited under the definition of the term CLC (Capravirine-like compound) but which further comprise a phosphonate group, *e.g.*, a phosphonate diester, phosphonamidate-ester prodrug, or a bis-phosphonamidate-ester (Jiang *et al.*, US 2002/0173490 A1).

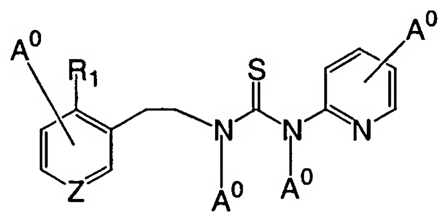
Whenever a compound described herein is substituted with more than one of the same designated group, *e.g.*, "R^1" or "R^{6a}", then it will be understood that the groups may be the same or different, *i.e.*, each group is independently selected. Wavy lines indicate the site of covalent bond attachments to the adjoining groups, moieties, or atoms.

Compounds of the invention are set forth in the Schemes, Examples, and claims below and include compounds of Formula I and Formula II. Formula I compounds have the general structure:

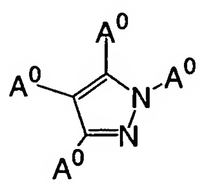


I

Compounds of the invention also include the Formulas:



where Z is CH or N,



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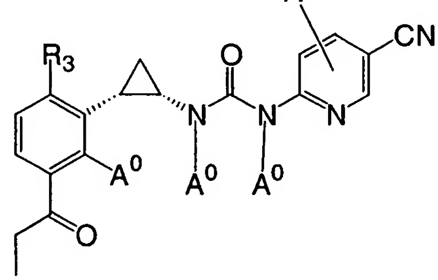

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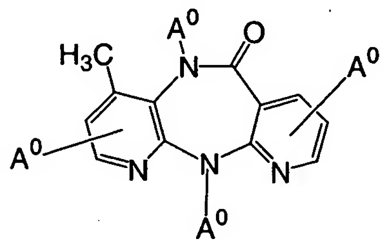

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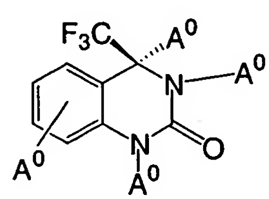

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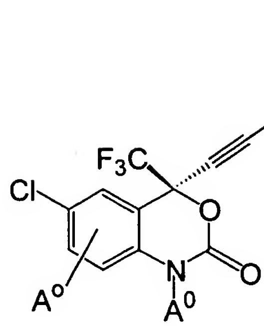
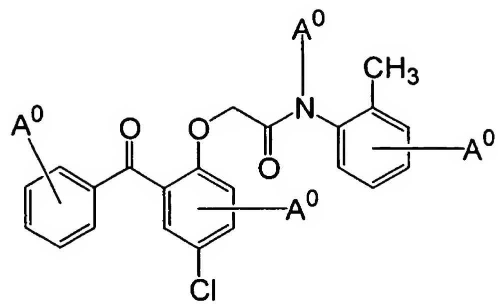
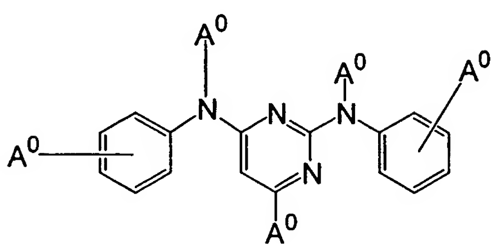
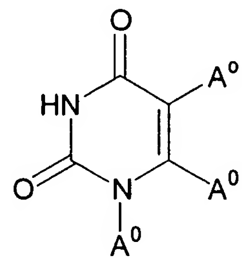
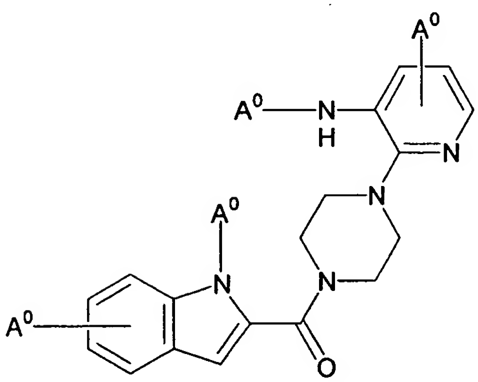
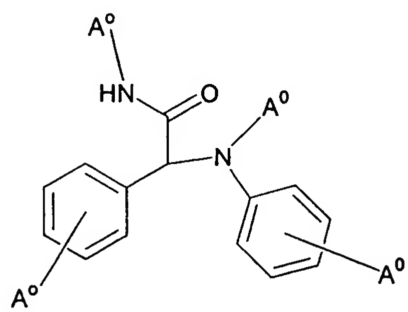
,

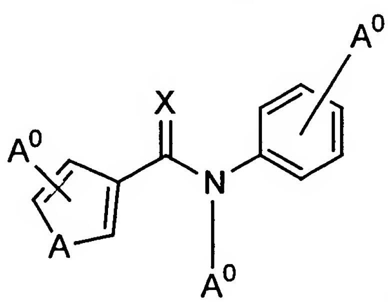
,

,

,

,

, and

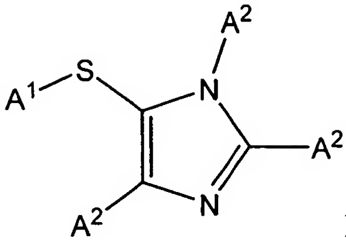


where A is O, S, or N(R^x) and X is O or S.

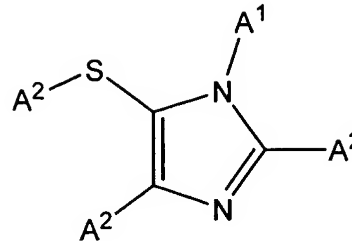
The above Formulas are substituted with one or more covalently attached A^0 groups, including simultaneous substitutions at any or all A^0.

A^0 is A^1, A^2 or W^3 with the proviso that the compound includes at least one A^1.

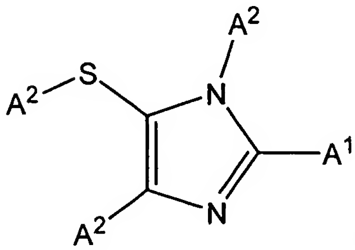
Exemplary embodiments of Formula I include Ia, Ib, Ic, and Id:



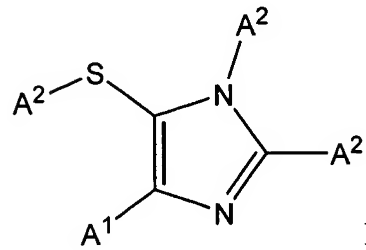
Ia



Ib



Ic

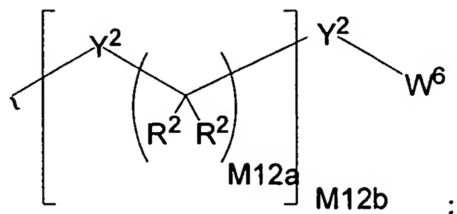


Id

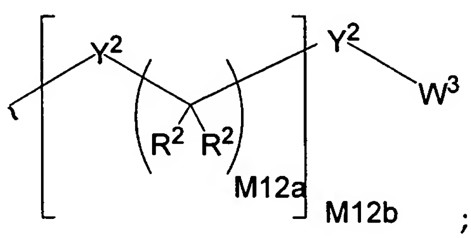
Whenever a compound described herein is substituted with more than one of the same designated group, *e.g.*, "R^1" or "R^{6a}", then it will be understood that the groups may be the same or different, *i.e.*, each group is independently selected.

Candidate compounds contain at least one A^1 (which in turn contains 1-3 A^3 groups) but also may contain at least one A^2 group.

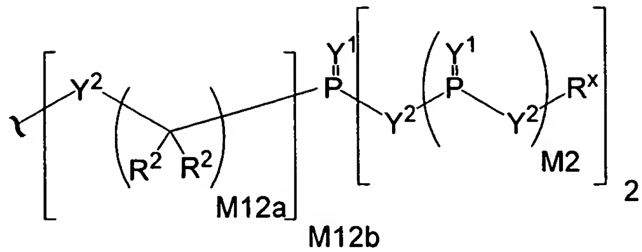
A^1 is:



A^2 is:



A^3 is:

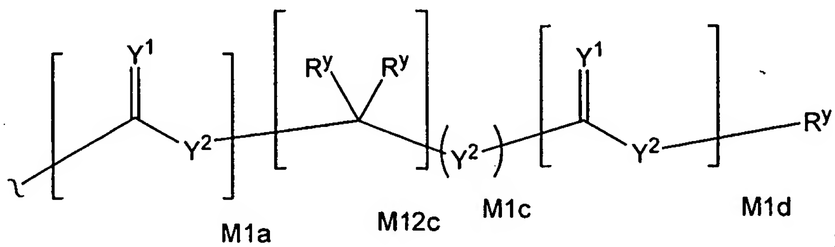


;

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, -$S(O)_{M2}$-, or -$S(O)_{M2}$-$S(O)_{M2}$-;

R^x is independently H, R^1, W^3, a protecting group, or the formula:



;

R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or an alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^1, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups. Alternatively, taken together at a carbon atom, two R^2 groups form a ring, *i.e.*, a spiro carbon. The ring may be, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. The ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or -NO_2;

R^{3b} is Y^1;

R^{3c} is -R^x, -$N(R^x)(R^x)$, -SR^x, -$S(O)R^x$, -$S(O)_2R^x$, -$S(O)(OR^x)$, -$S(O)_2(OR^x)$, -$OC(Y^1)R^x$, -$OC(Y^1)OR^x$, -$OC(Y^1)(N(R^x)(R^x))$, -$SC(Y^1)R^x$, -$SC(Y^1)OR^x$, -$SC(Y^1)(N(R^x)(R^x))$, -$N(R^x)C(Y^1)R^x$, -$N(R^x)C(Y^1)OR^x$, or -$N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is -$C(Y^1)R^x$, -$C(Y^1)OR^x$ or -$C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

W^7 is a heterocycle bonded through a nitrogen atom of said heterocycle and independently substituted with 0, 1 or 2 A^0 groups;

M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M1a, M1c, and M1d are independently 0 or 1; and

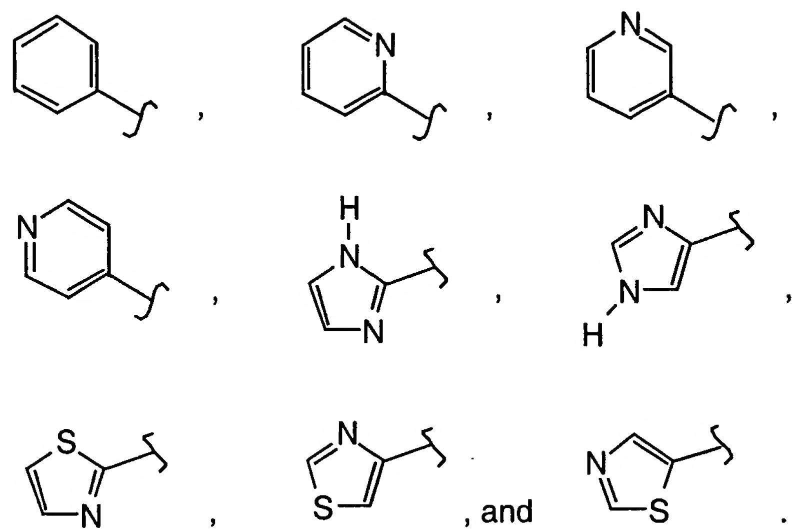
M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

W^5 carbocycles and W^5 heterocycles may be independently substituted with 0 to 3 R^2 groups. W^5 may be a saturated, unsaturated or aromatic ring comprising a mono- or bicyclic carbocycle or heterocycle. W^5 may have 3 to 10 ring atoms, *e.g.*, 3 to 7 ring atoms. The W^5 rings are saturated when containing 3 ring atoms, saturated or mono-unsaturated when containing 4 ring atoms, saturated, or mono- or di-unsaturated when containing 5 ring atoms, and saturated, mono- or di-unsaturated, or aromatic when containing 6 ring atoms.

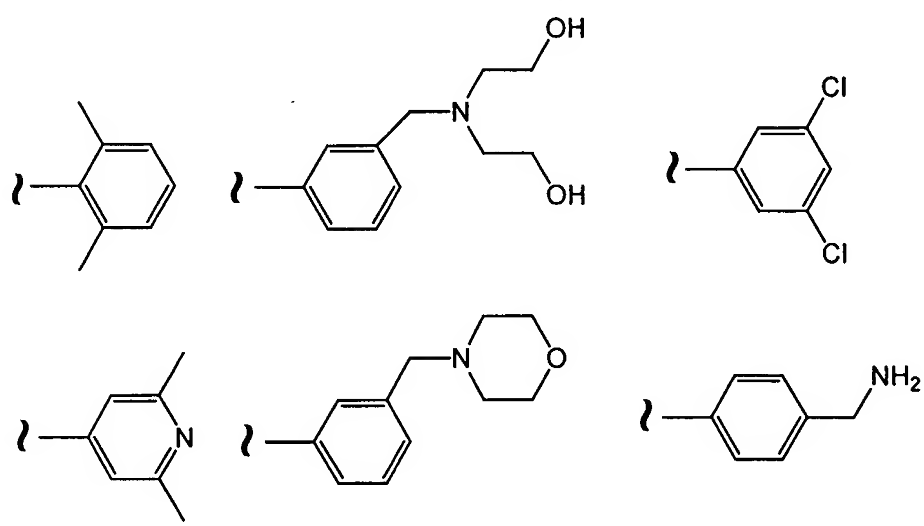
A W^5 heterocycle may be a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S) or a bicycle having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S). W^5 heterocyclic monocycles may have 3 to 6 ring atoms (2 to 5 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S); or 5 or 6 ring atoms (3 to 5 carbon atoms and 1 to 2 heteroatoms selected from N and S). W^5 heterocyclic bicycles have 7 to 10 ring atoms (6 to 9 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S) arranged as a bicyclo [4,5], [5,5], [5,6], or [6,6] system; or 9 to 10 ring atoms (8 to 9 carbon atoms and 1 to 2 hetero atoms selected from N and S) arranged as a bicyclo [5,6] or [6,6] system. The W^5 heterocycle may be bonded to Y^2 through a carbon, nitrogen, sulfur or other atom by a stable covalent bond.

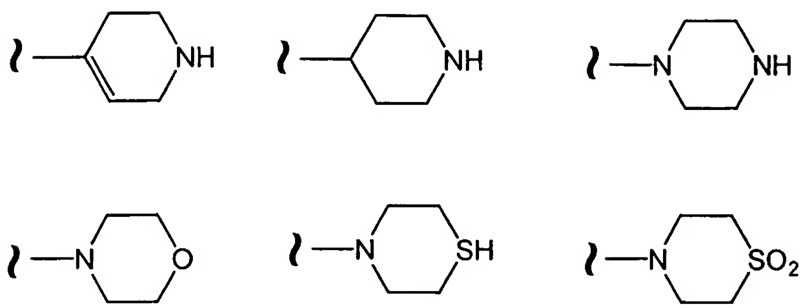
W^5 heterocycles include for example, pyridyl, dihydropyridyl isomers, piperidine, pyridazinyl, pyrimidinyl, pyrazinyl, s-triazinyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl,

pyrazolyl, isothiazolyl, furanyl, thiofuranyl, thienyl, and pyrrolyl. W^5 also includes, but is not limited to, examples such as:

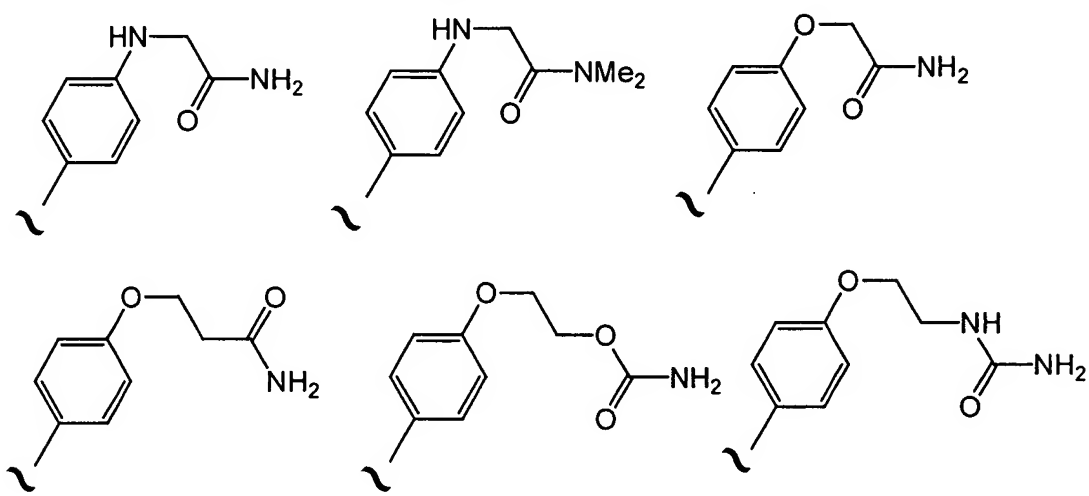


W^5 carbocycles and heterocycles may be independently substituted with 0 to 3 R^2 groups, as defined above. For example, substituted W^5 carbocycles include:





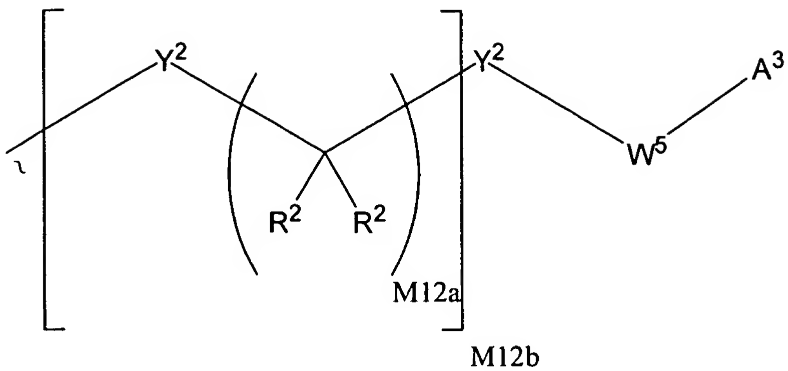
Examples of substituted phenyl carbocycles include:



Embodiments

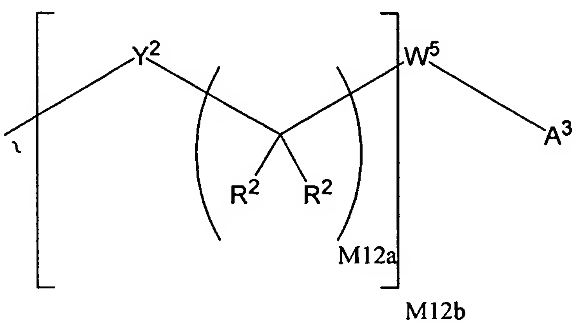
The following embodiments represent preferred choices for various substituents found on the candidate compounds of this invention. Each embodiment is to be construed as representing the enumerated substituent (or assembly of substituents) in combination with each and every other substituent that is not enumerated in the embodiment. For example, if W^3 is specified in an embodiment, then W^3 is locked but the remaining substituents can be set in any combination possible within the definition of A^3.

In an embodiment A^1 is

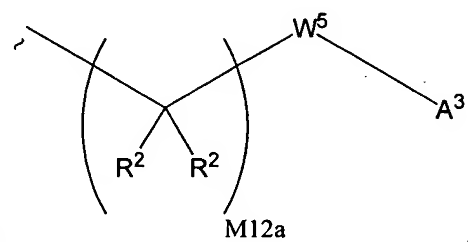


;

In an embodiment A^1 is

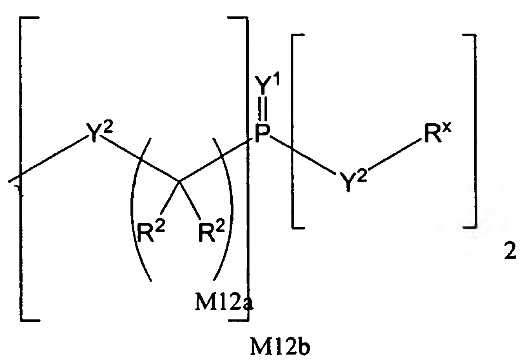


and

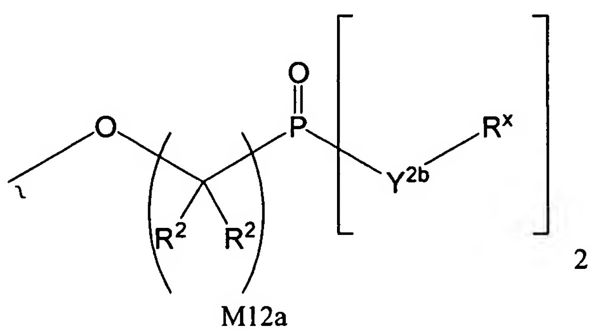


.

An embodiment of A^3 includes where M2 is 0, such as:

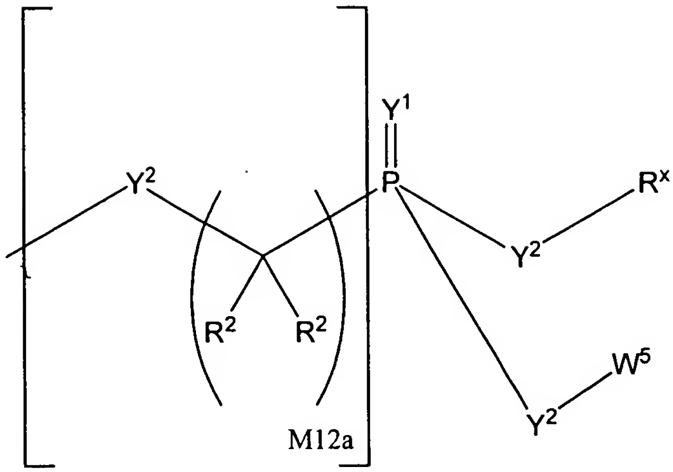


and where M12b is 1, Y^1 is oxygen, and Y^{2b} is oxygen (O) or nitrogen ($N(R^x)$) such as:



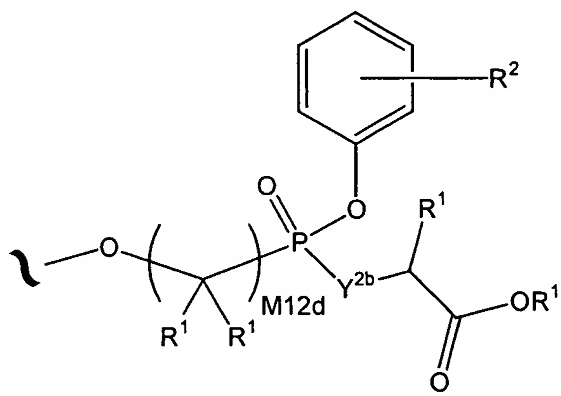
.

Another embodiment of A^3 is:

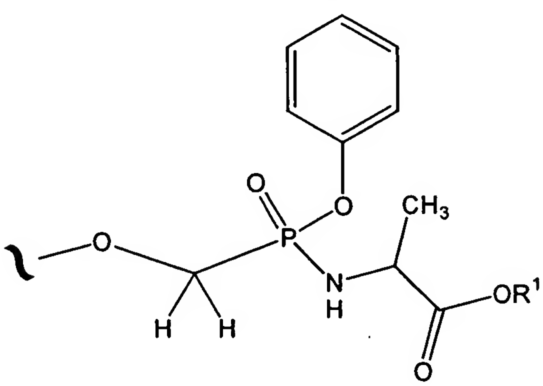


M12b

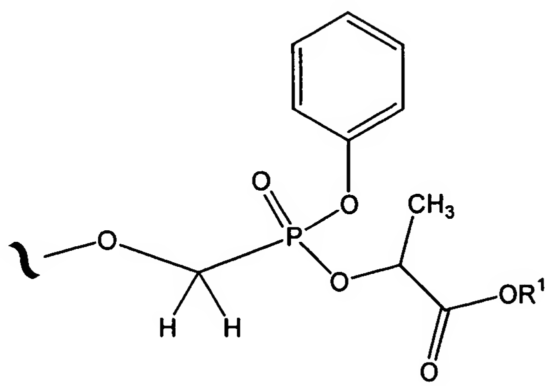
where W^5 is a carbocycle such as phenyl or substituted phenyl. Such embodiments include:



where Y^{2b} is O or $N(R^x)$; M12d is 1, 2, 3, 4, 5, 6, 7 or 8; and the phenyl carbocycle is substituted with 0 to 3 R^2 groups. Such embodiments of A^3 include phenyl phosphonamidate-alanate esters and phenyl phosphonate-lactate esters:

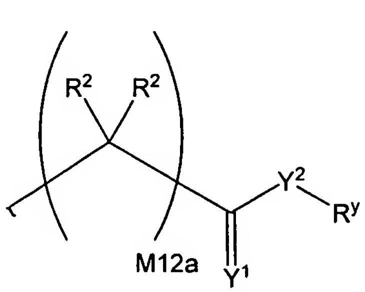


and

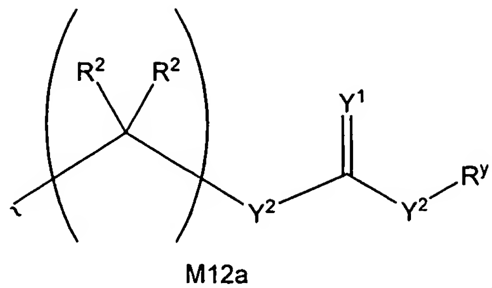


.

Embodiments of R^x include esters, carbamates, carbonates, thioesters, amides, thioamides, and urea groups:

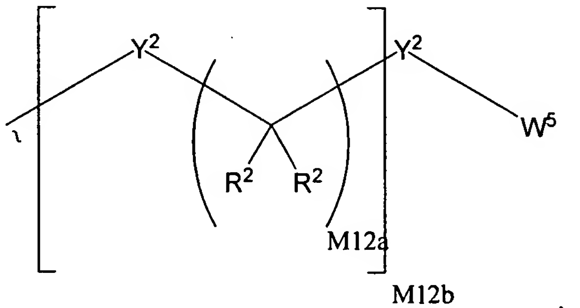


and



.

Embodiments of A^2 include where W^3 is W^5, such as:

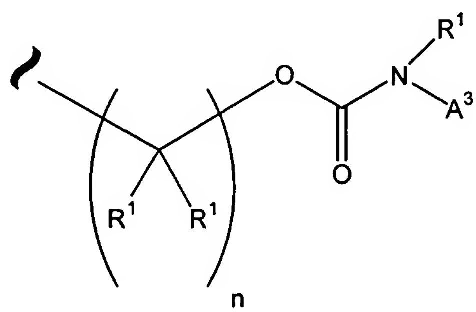


.

Alternatively, A^2 is phenyl, substituted phenyl, benzyl, substituted benzyl, pyridyl or substituted pyridyl.

In other embodiments W^4 may be R^4, W^{5a} is a carbocycle or heterocycle and W^{5a} is optionally and independently substituted with 1, 2, or 3 R^2 groups. For example, W^{5a} may be 3,5-dichlorophenyl.

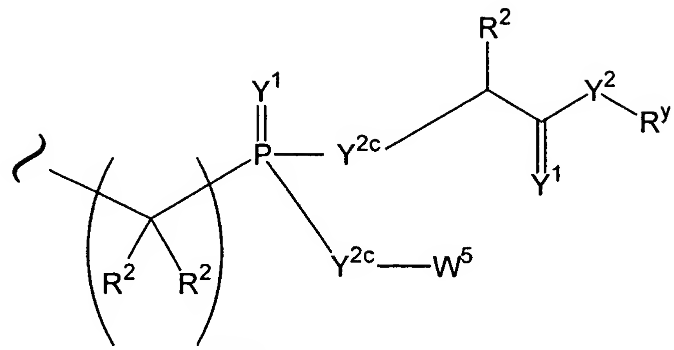
An embodiment of A^1 is:



;

n is an integer from 1 to 18;

An embodiment of A^3 optionally is of the formula:

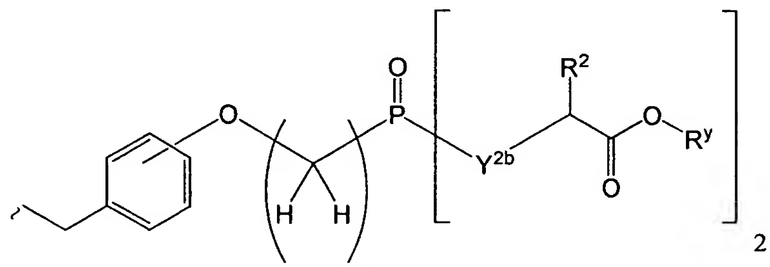


M12a

;

and Y^{2c} is O, $N(R^y)$ or S. For example, R^1 may be H and n may be 1.

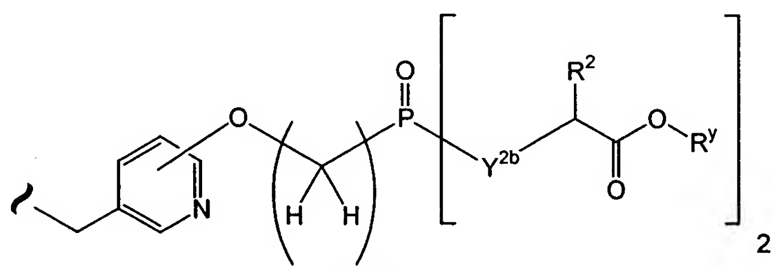
An embodiment of A^1 optionally comprises a phosphonate group attached to an imidazole nitrogen through a heterocycle linker, such as:



M12d

;

and



M12d

;

where Y^{2b} is O or $N(R^2)$; and M12d is 1, 2, 3, 4, 5, 6, 7 or 8. The A^3 unit may be attached at any of the W^5 carbocycle or heterocycle ring atoms, *e.g.*, ortho, meta, or para on a disubstituted W^5.

A_1 optionally is $-(X_2-(C(R_2)(R_2))_{m1}-X_3)_{m1}-W_3$, and W_3 is substituted with 1 to 3 A_3 groups.

A_2 optionally is $-(X_2-(C(R_2)(R_2))_{m1}-X_3)_{m1}-W_3$.

A_3 optionally is $-(X_2-(C(R_2)(R_2))_{m1}-X_3)_{m1}-P(Y_1)(Y_1R_{6a})(Y_1R_{6a})$.

X_2 and X_3 optionally are independently a bond, -O-, -N(R_2)-, -N(OR_2)-, -N(N(R_2)(R_2))-, -S-, -SO-, or -SO2-.

Each Y_1 optionally is independently O, N(R_2), N(OR_2), or N(N(R_2)(R_2)), wherein each Y_1 is bound by two single bonds or one double bond.

R_1 optionally is independently H or alkyl of 1 to 12 carbon atoms.

R_2 optionally is independently H, R_3 or R_4 wherein each R_4 is independently substituted with 0 to 3 R_3 groups.

R_3 optionally is independently F, Cl, Br, I, -CN, N_3, -NO_2, -OR_{6a}, -OR_1, -N(R_1)2, -N(R_1)(R_{6b}), -N(R_{6b})2, -SR_1, -SR_{6a}, -S(O)R_1, -S(O)2R_1, -S(O)OR_1, -S(O)OR_{6a}, -S(O)2OR_1, -S(O)2OR_{6a}, -C(O)OR_1, -C(O)R_{6c}, -C(O)OR_{6a}, -OC(O)R_1, -N(R_1)(C(O)R_1), -N(R_{6b})(C(O)R_1), -N(R_1)(C(O)OR_1), -N(R_{6b})(C(O)OR_1), -C(O)N(R_1)2, -C(O)N(R_{6b})(R_1), -C(O)N(R_{6b})2, -C(NR_1)(N(R_1)2), -C(N(R_{6b}))(N(R_1)2), -C(N(R_1))(N(R_1)(R_{6b})), -C(N(R_{6b}))(N(R_1)(R_{6b})), -C(N(R_1))(N(R_{6b})2), -C(N(R_{6b}))(N(R_{6b})2), -N(R_1)C(N(R_1))(N(R_1)2), -N(R_1)C(N(R_1))(N(R_1)(R_{6b})), -N(R_1)C(N(R_{6b}))(N(R_1)2), -N(R_{6b})C(N(R_1))(N(R_1)2), -N(R_{6b})C(N(R_{6b}))(N(R_1)2), -N(R_{6b})C(N(R_1))(N(R_1)(R_{6b})), -N(R_1)C(N(R_{6b}))(N(R_1)(R_{6b})), -N(R_1)C(N(R_1))(N(R_{6b})2), -N(R_{6b})C(N(R_{6b}))(N(R_1)(R_{6b})), -N(R_{6b})C(N(R_1))(N(R_{6b})2), -N(R_1)C(N(R_{6b}))(N(R_{6b})2), -N(R_{6b})C(N(R_{6b}))(N(R_{6b})2), =O, =S, =N(R_1), =N(R_{6b}) or W_5.

R_4 optionally is independently alkyl of 1 to 12 carbon atoms, alkenyl of 2 to 12 carbon atoms, or alkynyl of 2 to 12 carbon atoms.

R_5 optionally is independently R_4 wherein each R_4 is substituted with 0 to 3 R_3 groups; or R_5 is independently alkylene of 1 to 12 carbon atoms, alkenylene of 2 to 12 carbon atoms, or alkynylene of 2-12 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R_3 groups.

R_{6a} is independently H or an ether- or ester-forming group.

R_{6b} is independently H, a protecting group for amino or the residue of a carboxyl-containing compound.

R_{6c} is independently H or the residue of an amino-containing compound.

W_4 is R_5, -C(Y_1)R_5, -C(Y_1)W_5, -SO_2R_5, or -SO_2W_5.

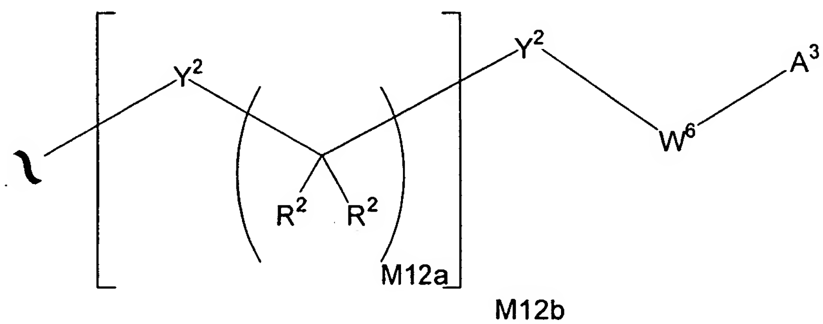
W_5 is carbocycle or heterocycle wherein W_5 is independently substituted with 0 to 3 R_2 groups.

m1 is independently an integer from 0 to 12, wherein the sum of all m1's within each individual embodiment of A_1, A_2 or A_3 is 12 or less.

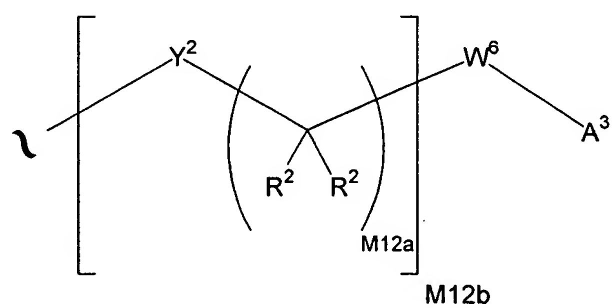
m2 is independently an integer from 0 to 2.

In another embodiment A_1 is $-(C(R_2)(R_2))_{m1}-W_3$, wherein W_3 is substituted with 1 A_3 group, A_2 is $-(C(R_2)(R_2))_{m1}-W_3$, and A_3 is $-(C(R_2)(R_2))_{m1}P(Y_1)(Y_1R_{6a})(Y_1R_{6a})$.

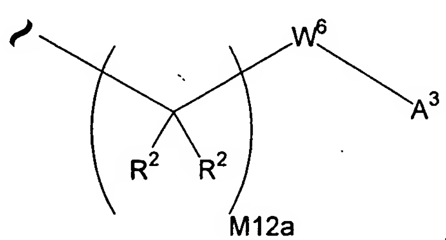
In an embodiment A^1 is of the formula:



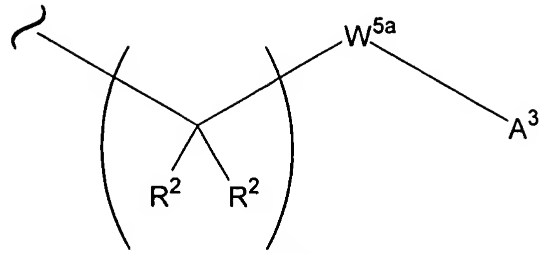
In an embodiment A^1 is of the formula:



In an embodiment A^1 is of the formula:



In an embodiment A^1 is of the formula:

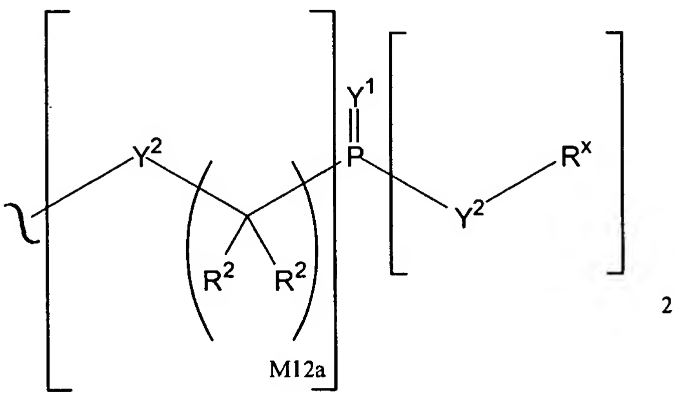


M12a ;

and W^{5a} is a carbocycle or a heterocycle where W^{5a} is independently substituted with 0 or 1 R^2 groups.

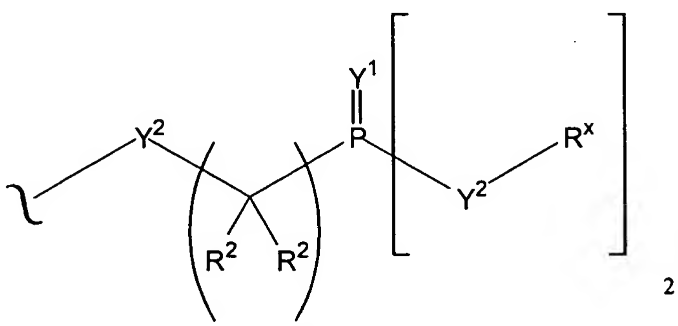
In an embodiment M12a is 1.

In an embodiment A^3 is of the formula:



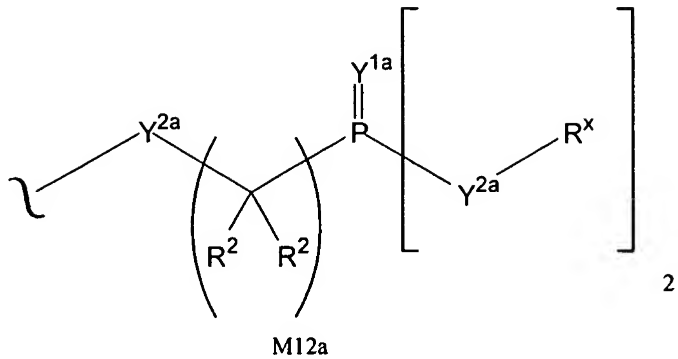
M12b .

In an embodiment A^3 is of the formula:



M12a .

In an embodiment A^3 is of the formula:

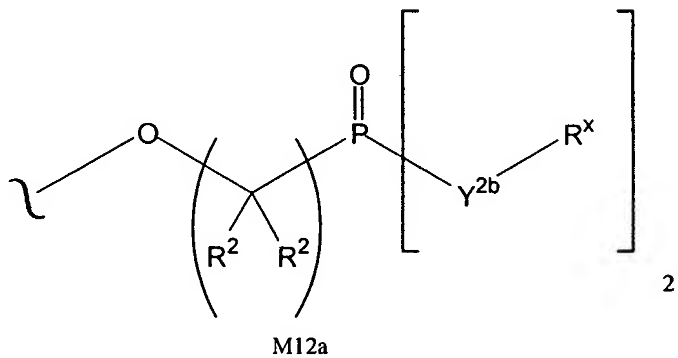


;

Y^{1a} is O or S; and

Y^{2a} is O, $N(R^x)$ or S.

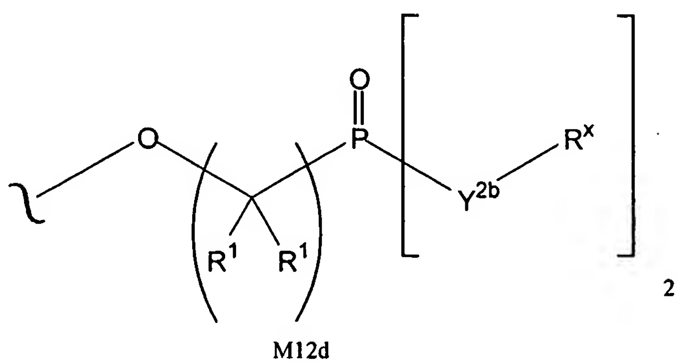
In an embodiment A^3 is of the formula:



;

and Y^{2b} is O or $N(R^x)$.

In an embodiment A^3 is of the formula:

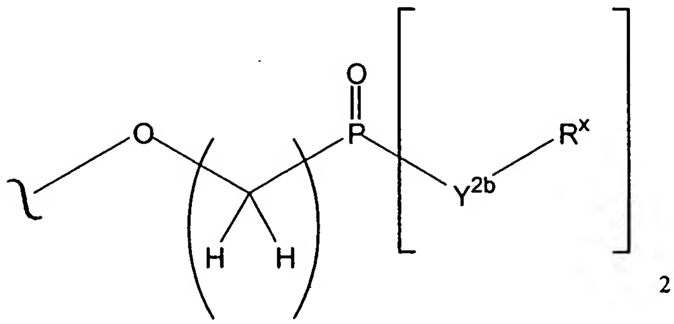


;

Y^{2b} is O or $N(R^x)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In an embodiment A^3 is of the formula:



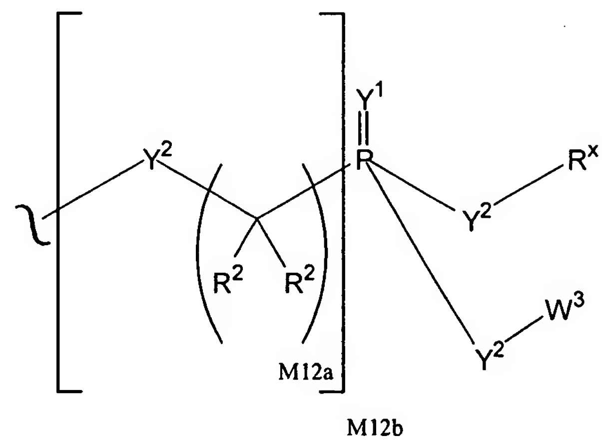
M12d ;

Y^{2b} is O or N(R^x); and

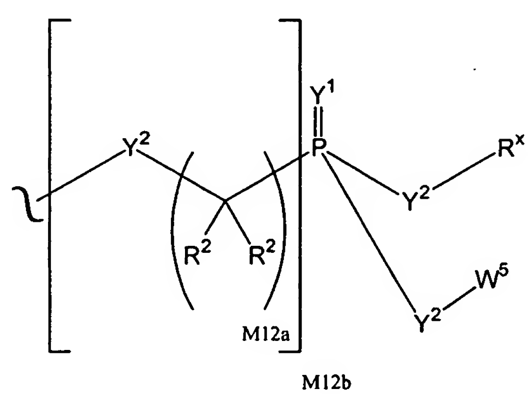
M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In an embodiment M12d is 1.

In an embodiment A^3 is of the formula:

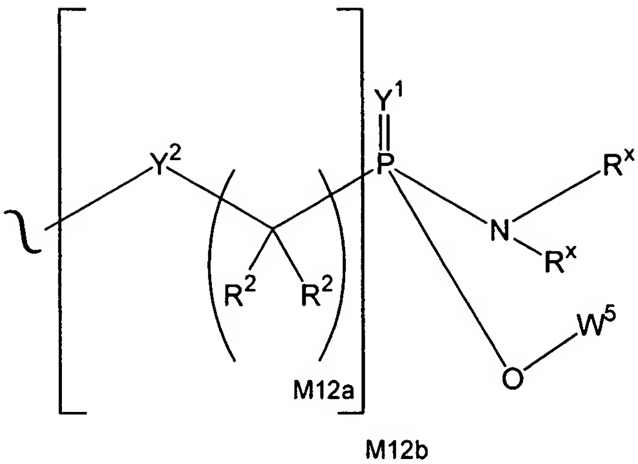


In an embodiment A^3 is of the formula:



In an embodiment W^5 is a carbocycle.

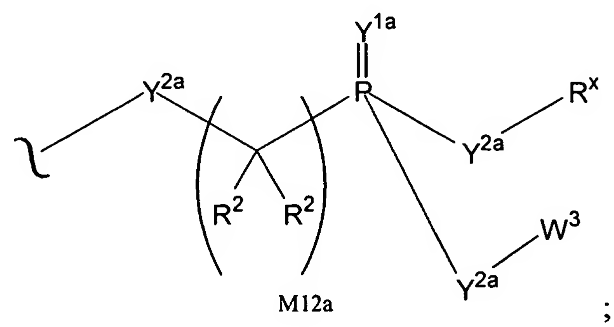
In an embodiment A^3 is of the formula:



In an embodiment W^5 is phenyl.

In an embodiment M12b is 1.

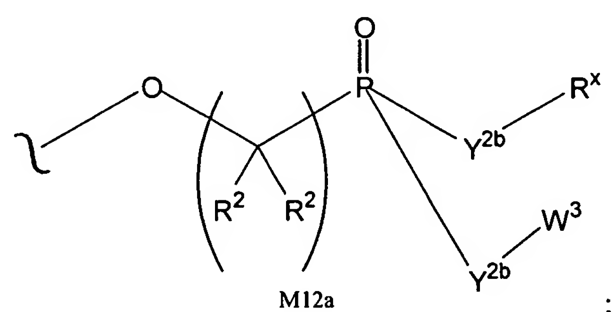
In an embodiment A^3 is of the formula:



Y^{1a} is O or S; and

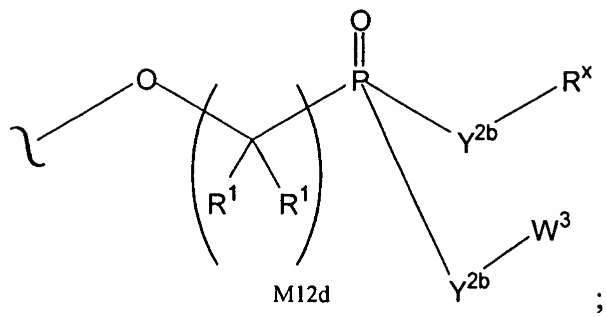
Y^{2a} is O, $N(R^x)$ or S.

In an embodiment A^3 is of the formula:



and Y^{2b} is O or $N(R^x)$.

In an embodiment A^3 is of the formula:



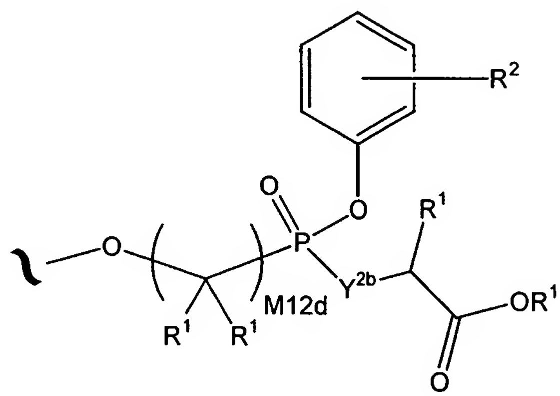
Y^{2b} is O or $N(R^x)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In an embodiment R^1 is H.

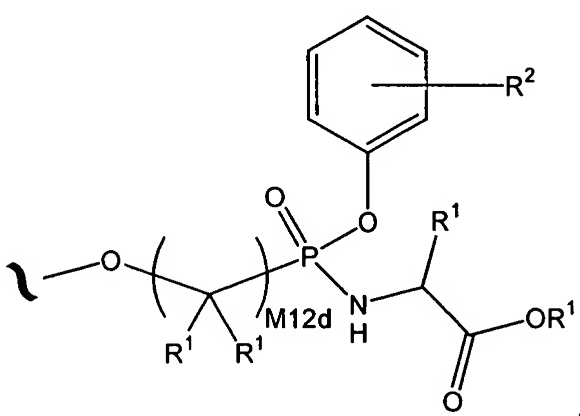
In an embodiment M12d is 1.

In an embodiment A^3 is of the formula:

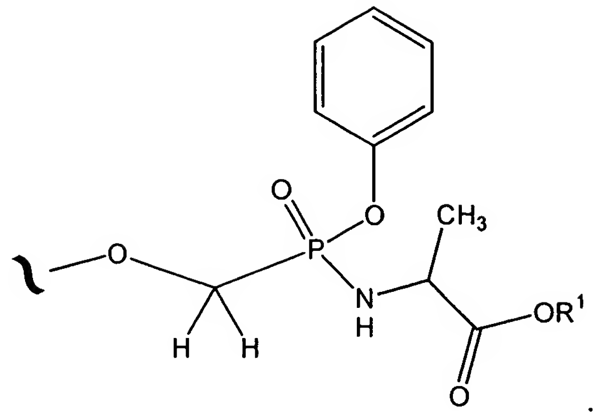


wherein the phenyl carbocycle is substituted with 0 to 3 R^2 groups.

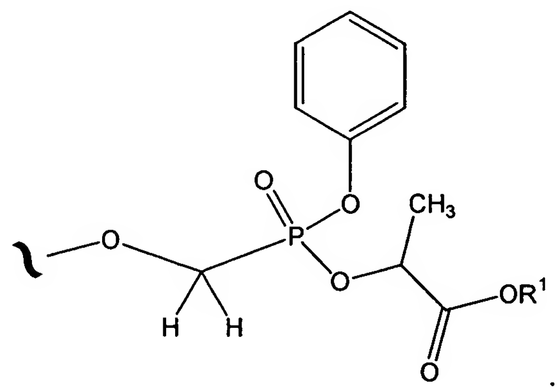
In an embodiment A^3 is of the formula:



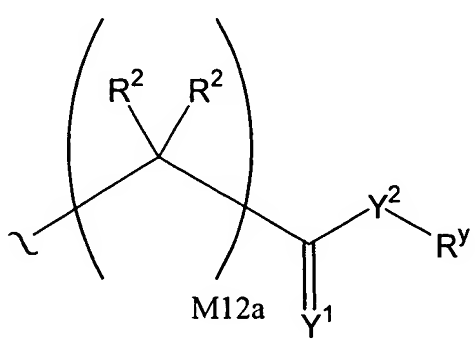
In an embodiment A^3 is of the formula:



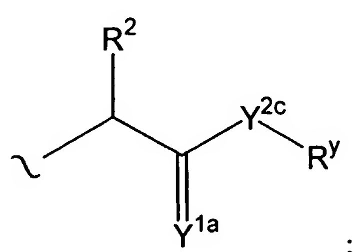
In an embodiment A^3 is of the formula:



In an embodiment R^x is of the formula:



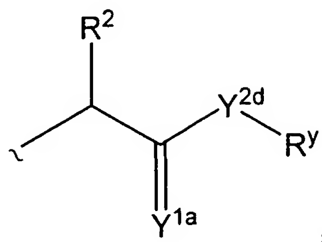
In an embodiment R^x is of the formula:



Y^{1a} is O or S; and

Y^{2c} is O, $N(R^y)$ or S.

In an embodiment R^x is of the formula:

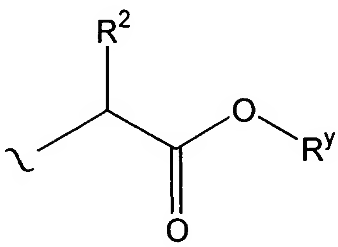


;

Y^{1a} is O or S; and

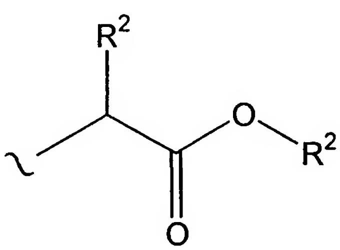
Y^{2d} is O or $N(R^y)$.

In an embodiment R^x is of the formula:



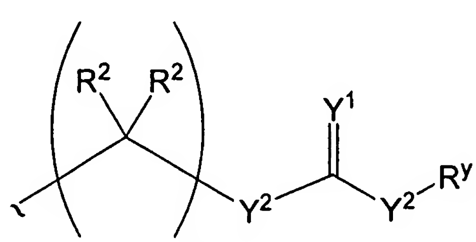
.

In an embodiment R^x is of the formula:



.

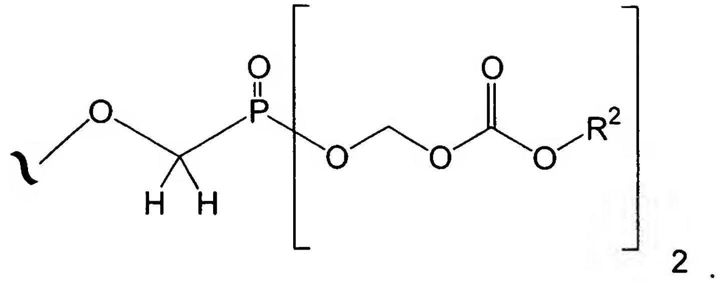
In an embodiment R^x is of the formula:



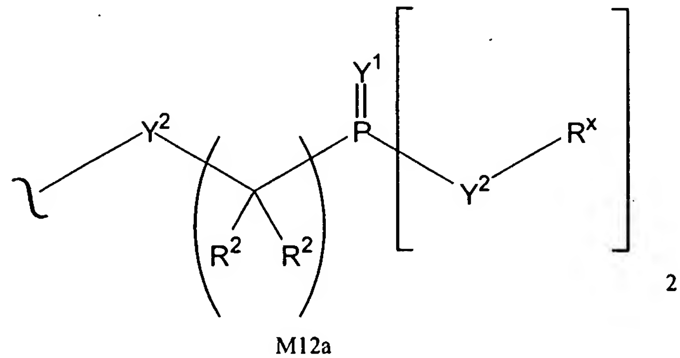
M12a

.

In an embodiment A^3 is of the formula:

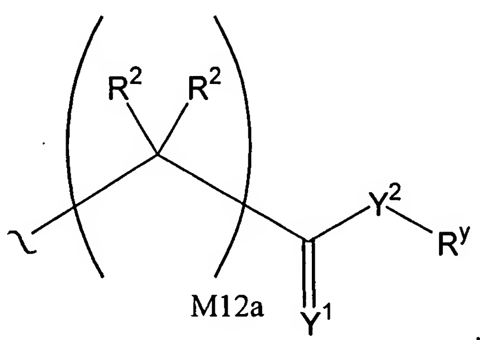


In an embodiment A^3 is of the formula:

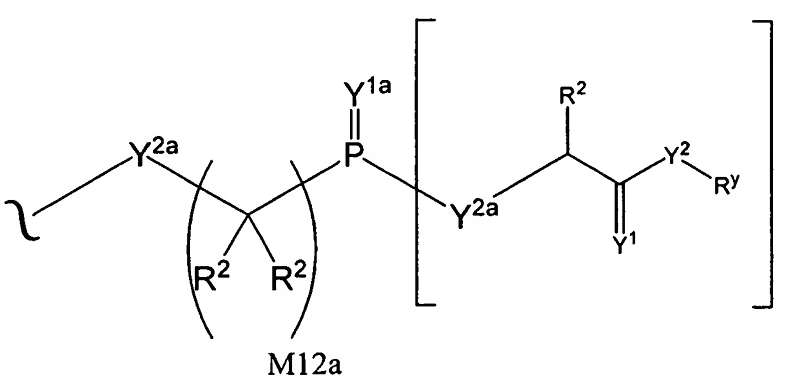


; and

R^x is of the formula:



In an embodiment A^3 is of the formula:

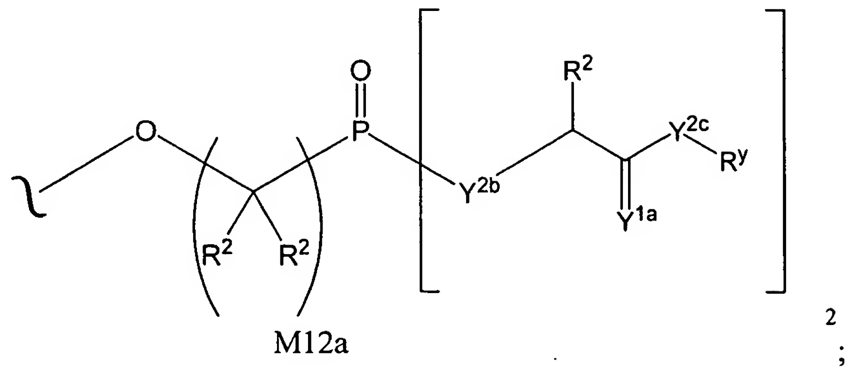


;

Y^{1a} is O or S; and

Y^{2a} is O, $N(R^2)$ or S.

In an embodiment A^3 is of the formula:

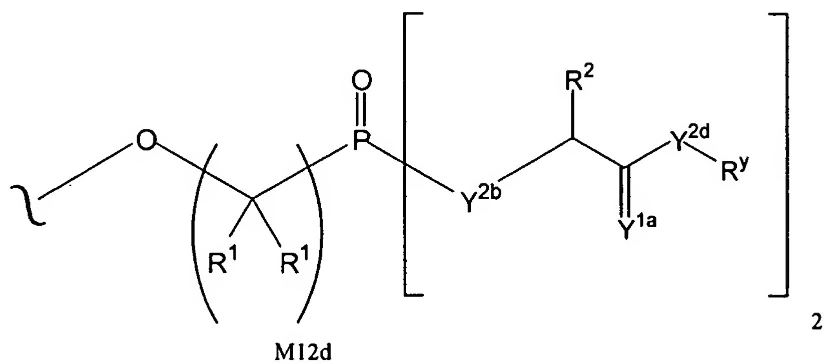


Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$; and

Y^{2c} is O, $N(R^y)$ or S.

In an embodiment A^3 is of the formula:



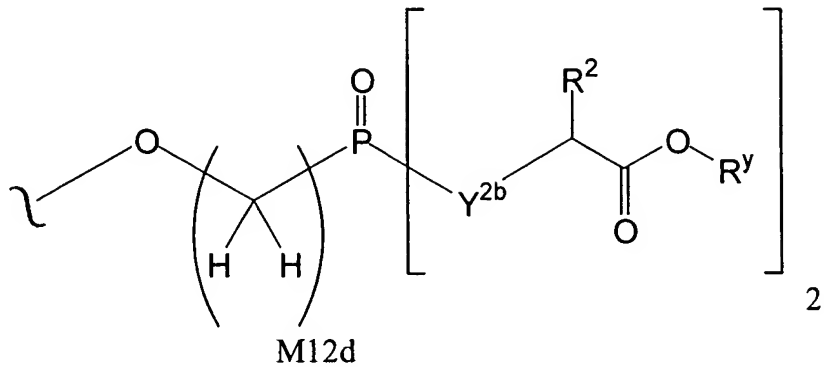
Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$;

Y^{2d} is O or $N(R^y)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In an embodiment A^3 is of the formula:

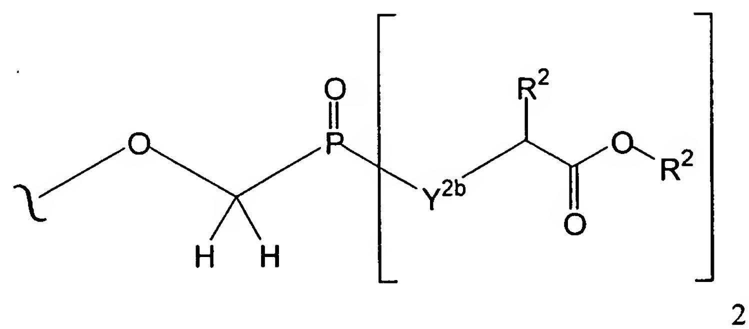


;

Y^{2b} is O or $N(R^2)$; and

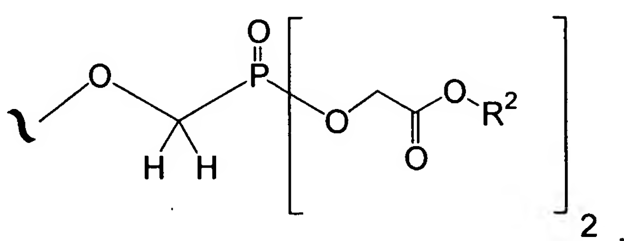
M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In an embodiment A^3 is of the formula:

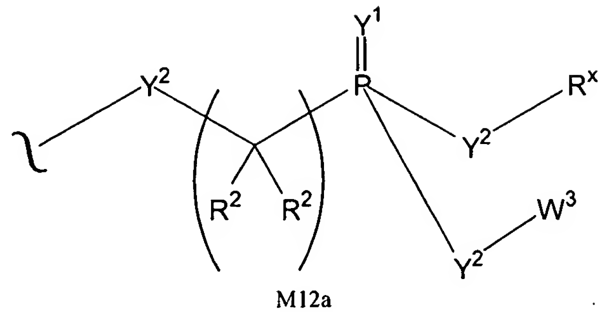


and Y^{2b} is O or $N(R^2)$.

In an embodiment A^3 is of the formula:

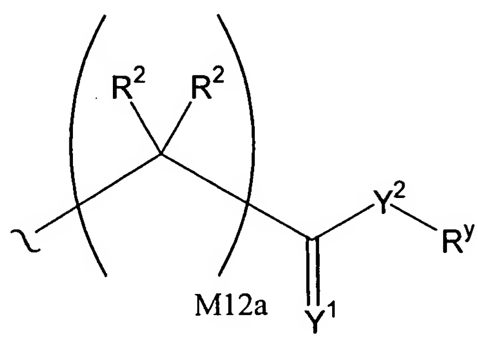


In an embodiment A^3 is of the formula:



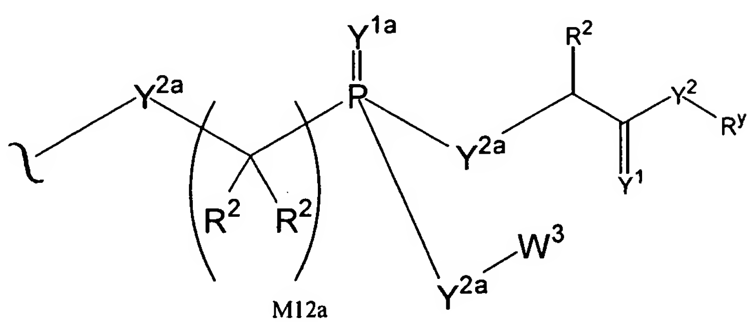
; and

R^x is of the formula:



.

In an embodiment A^3 is of the formula:

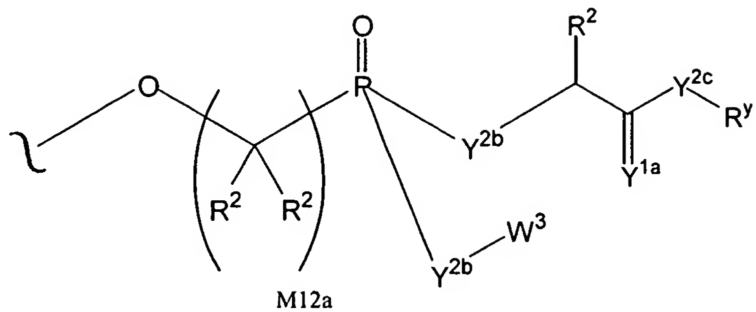


;

Y^{1a} is O or S; and

Y^{2a} is O, $N(R^2)$ or S.

In an embodiment A^3 is of the formula:



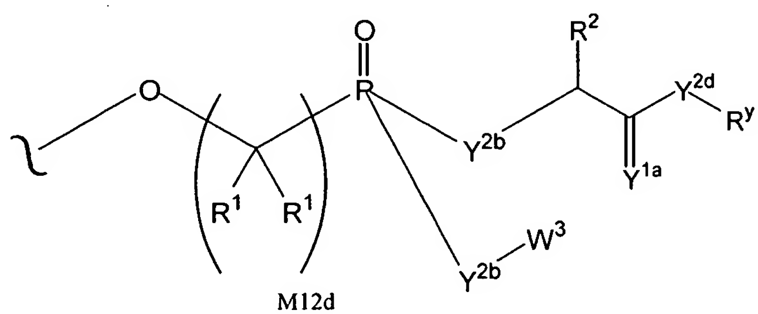
;

Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$; and

Y^{2c} is O, $N(R^y)$ or S.

In an embodiment A^3 is of the formula:



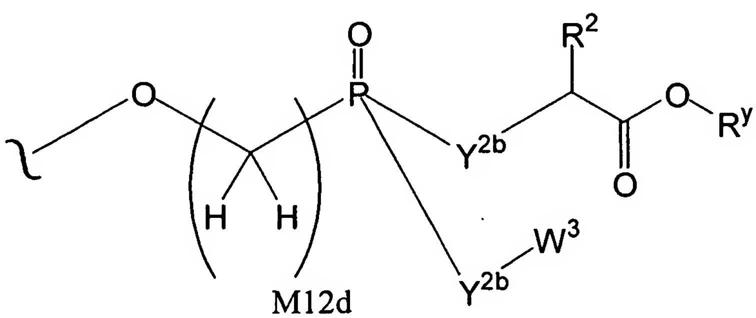
Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$;

Y^{2d} is O or $N(R^y)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In an embodiment A^3 is of the formula:

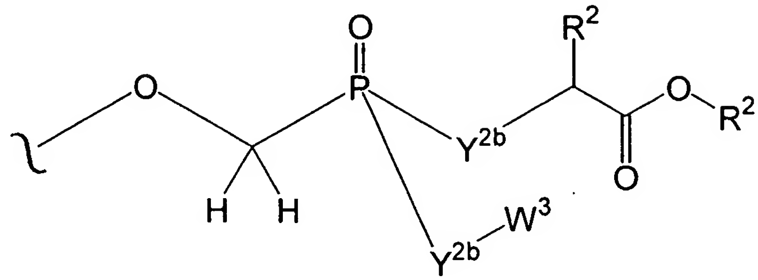


;

Y^{2b} is O or $N(R^2)$; and

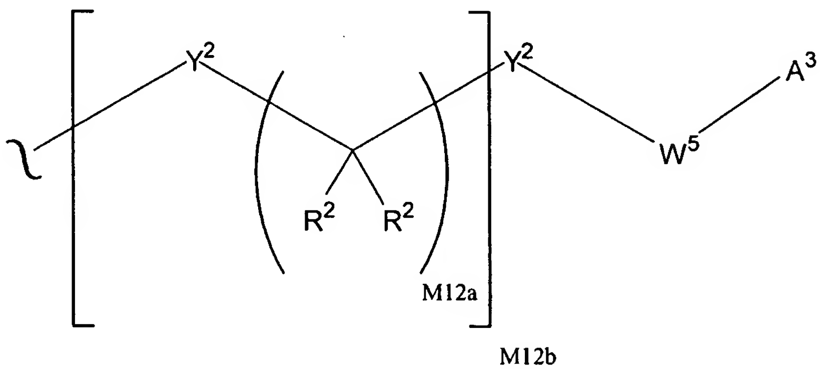
M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In an embodiment A^3 is of the formula:



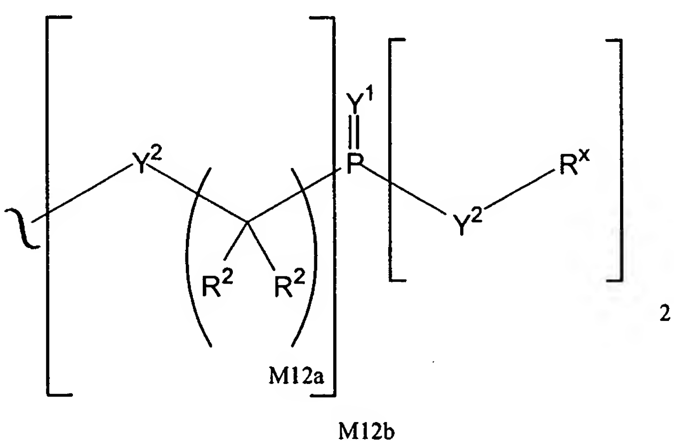
and Y^{2b} is O or $N(R^2)$.

In an embodiment A^1 is of the formula:



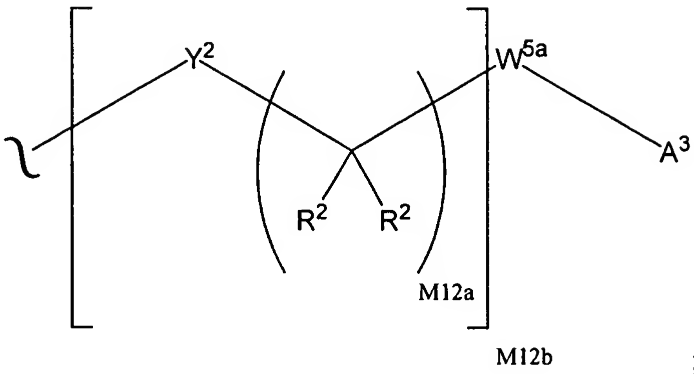
; and

A^3 is of the formula:

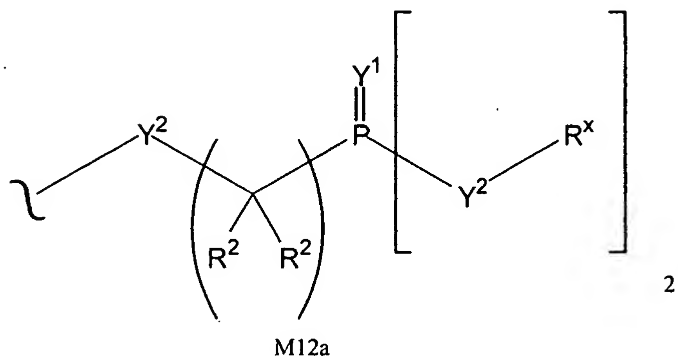


.

In an embodiment A^1 is of the formula:

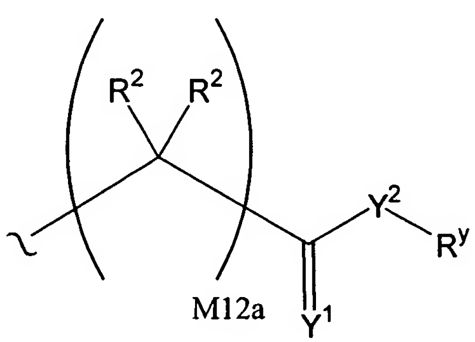


A^3 is of the formula:

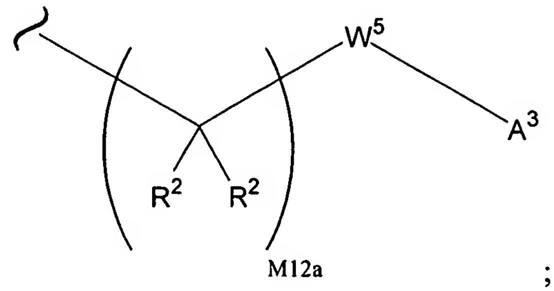


; and

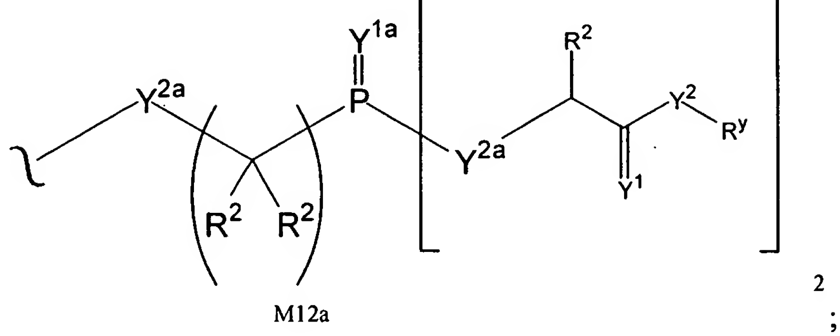
R^x is of the formula:



In an embodiment A^1 is of the formula:



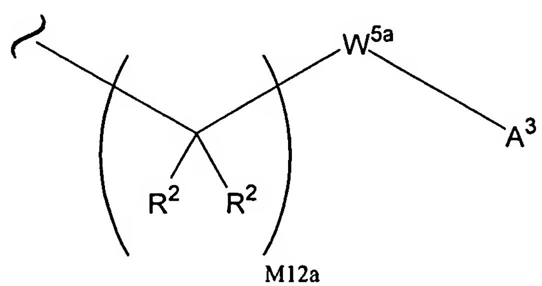
A^3 is of the formula:



Y^{1a} is O or S; and

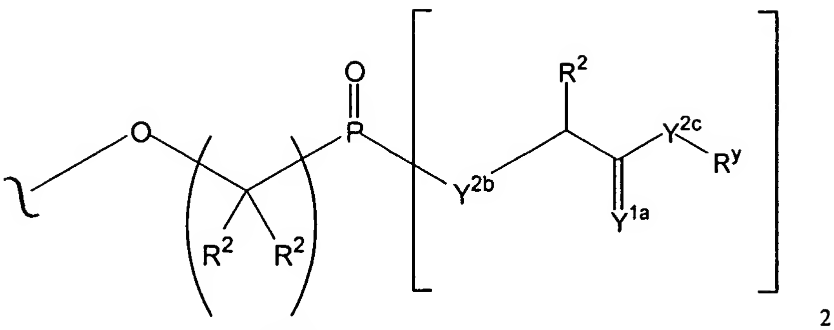
Y^{2a} is O, $N(R^2)$ or S.

In an embodiment A^1 is of the formula:



W^{5a} is a carbocycle independently substituted with 0 or 1 R^2 groups;

A^3 is of the formula:



M12a

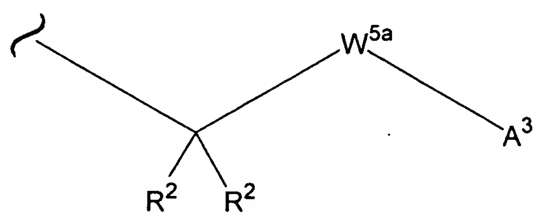
;

Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$; and

Y^{2c} is O, $N(R^y)$ or S.

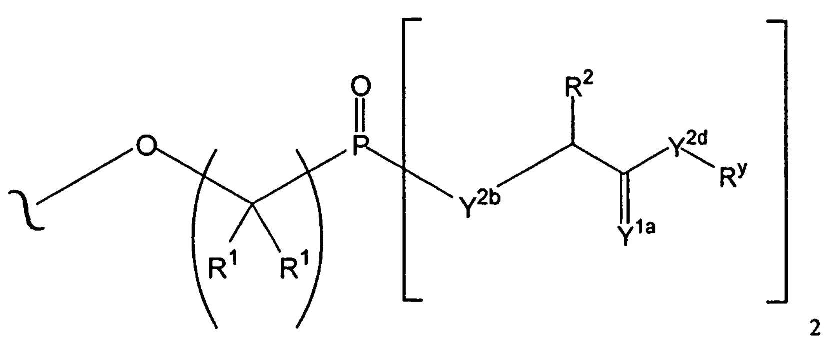
In an embodiment A^1 is of the formula:



;

W^{5a} is a carbocycle independently substituted with 0 or 1 R^2 groups;

A^3 is of the formula:



M12d

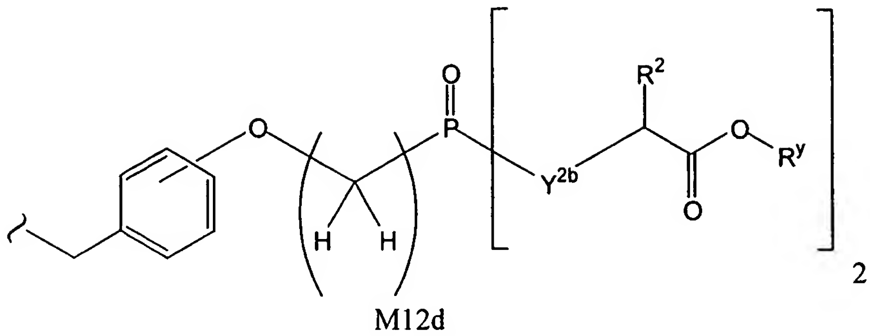
Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$;

Y^{2d} is O or $N(R^y)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

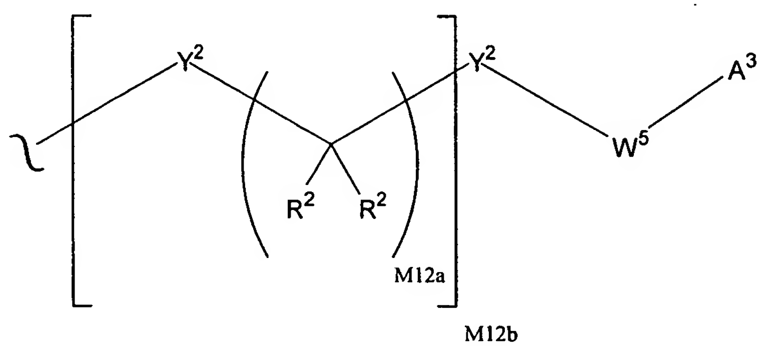
In an embodiment A^1 is of the formula:



Y^{2b} is O or $N(R^2)$; and

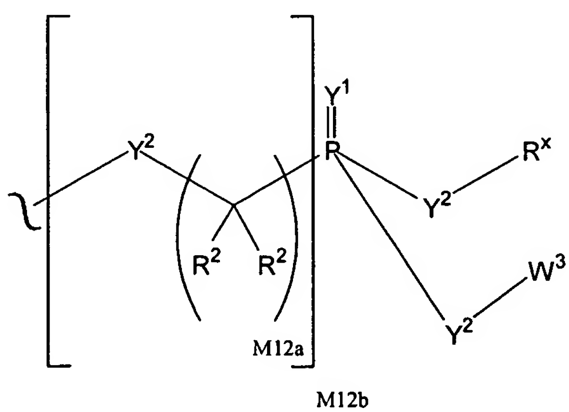
M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In an embodiment A^1 is of the formula:



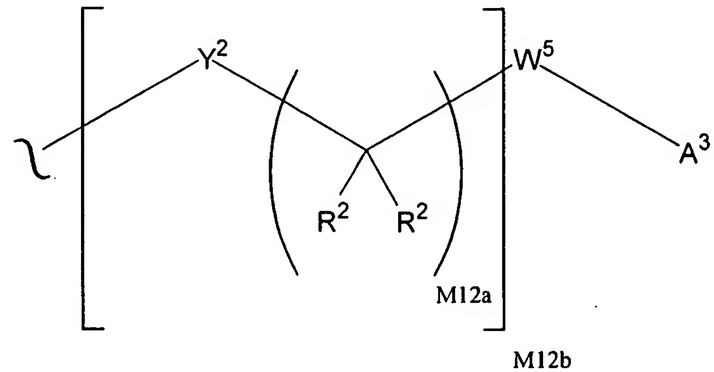
; and

A^3 is of the formula:



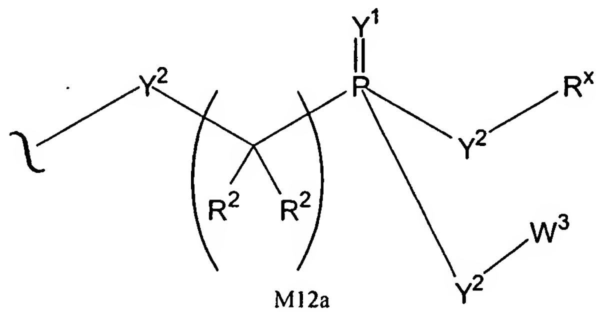
.

In an embodiment A^1 is of the formula:



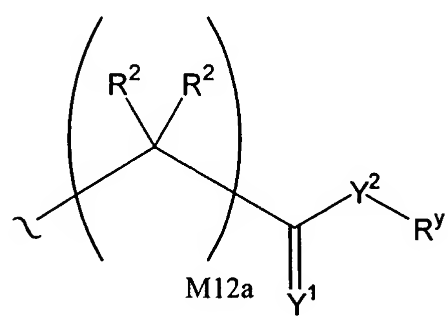
;

A^3 is of the formula:



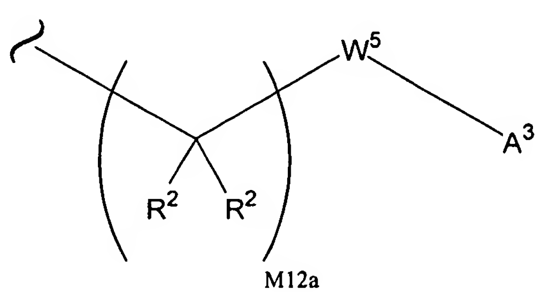
; and

R^x is of the formula:



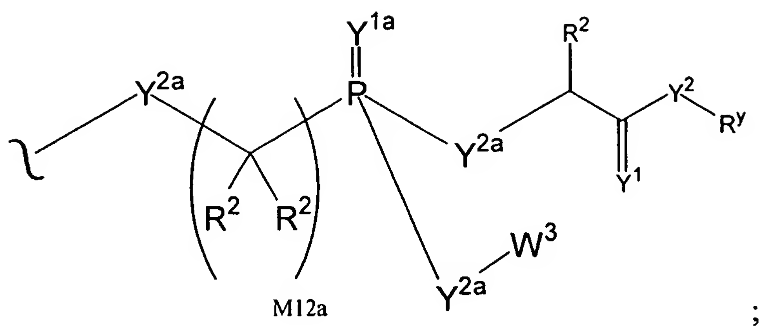
.

In an embodiment A^1 is of the formula:



;

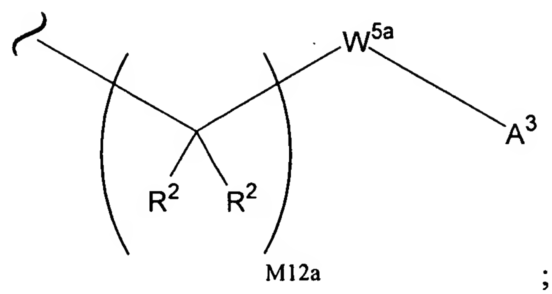
A^3 is of the formula:



Y^{1a} is O or S; and

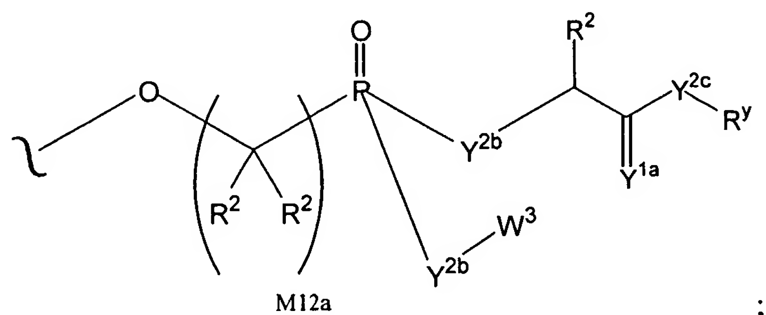
Y^{2a} is O, $N(R^2)$ or S.

In an embodiment A^1 is of the formula:



W^{5a} is a carbocycle independently substituted with 0 or 1 R^2 groups;

A^3 is of the formula:

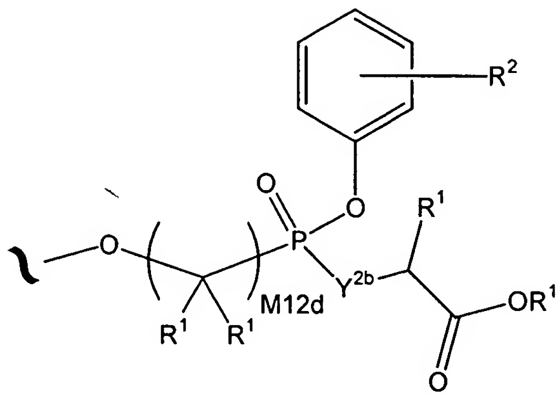


Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$; and

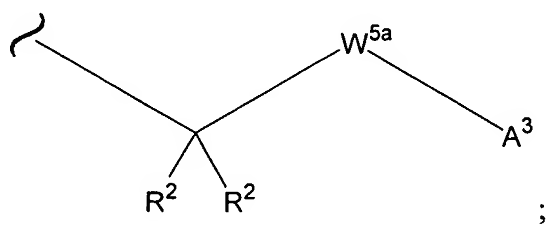
Y^{2c} is O, $N(R^y)$ or S.

In an embodiment A^3 is of the formula:



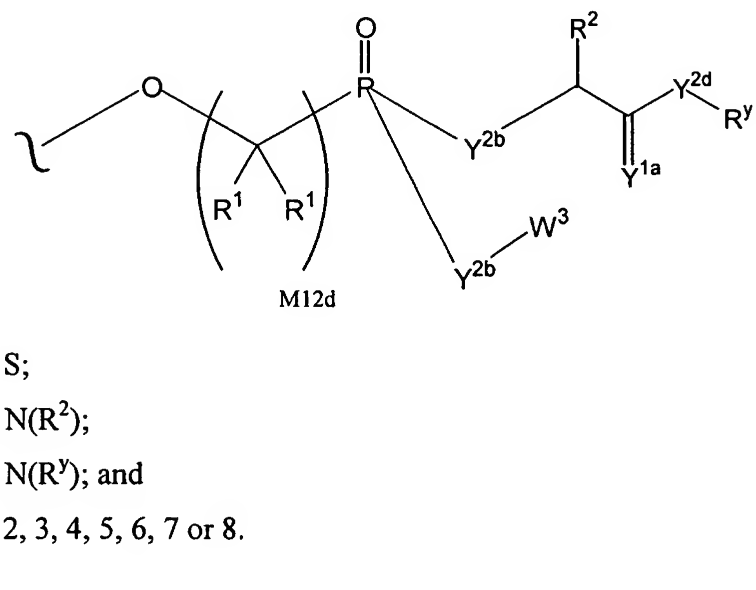
wherein the phenyl carbocycle is substituted with 0 to 3 R^2 groups.

In an embodiment A^1 is of the formula:



W^{5a} is a carbocycle or heterocycle where W^{5a} is independently substituted with 0 or 1 R^2 groups;

A^3 is of the formula:



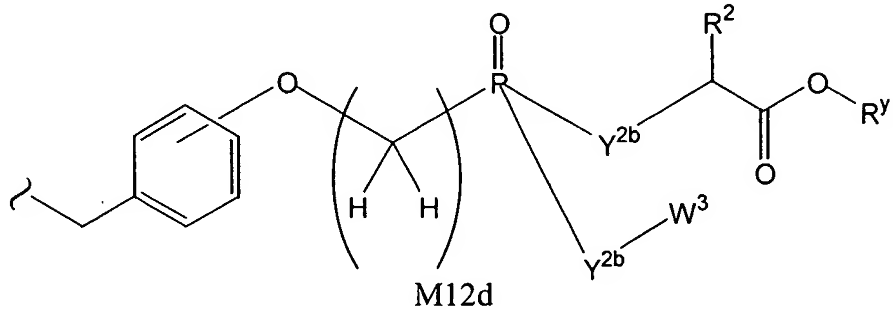
Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$;

Y^{2d} is O or $N(R^y)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

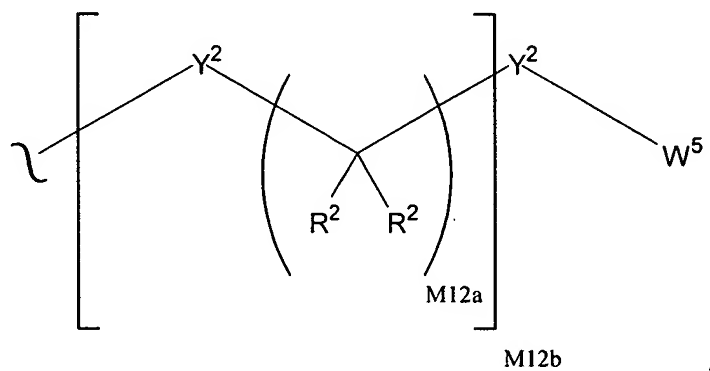
In an embodiment A^1 is of the formula:



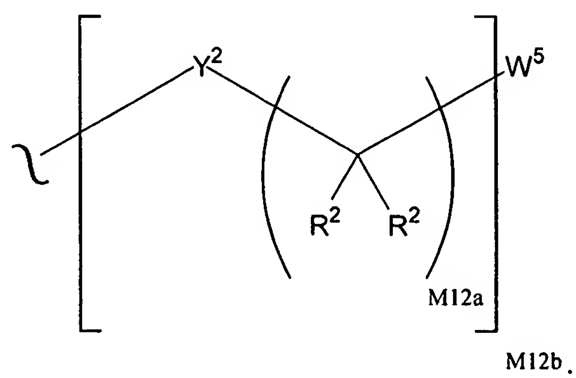
Y^{2b} is O or $N(R^2)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In an embodiment A^2 is of the formula:



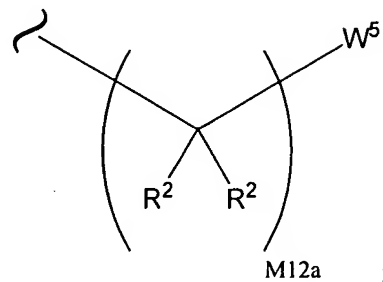
In an embodiment A^2 is of the formula:



In an embodiment M12b is 1.

In an embodiment M12b is 0, Y^2 is a bond and W^5 is a carbocycle or heterocycle where W^5 is optionally and independently substituted with 1, 2, or 3 R^2 groups.

In an embodiment A^2 is of the formula:



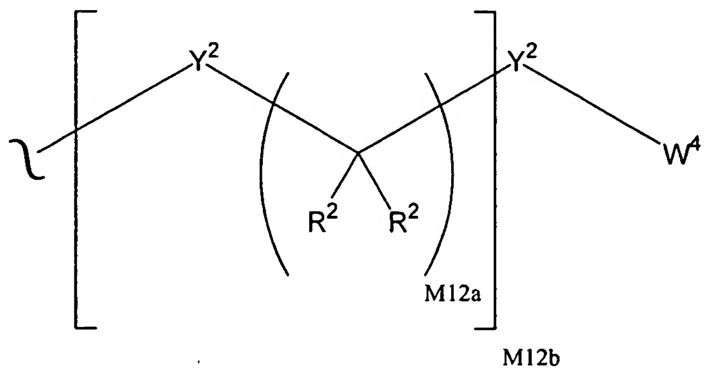
;

and W^{5a} is a carbocycle or heterocycle where W^{5a} is optionally and independently substituted with 1, 2, or 3 R^2 groups.

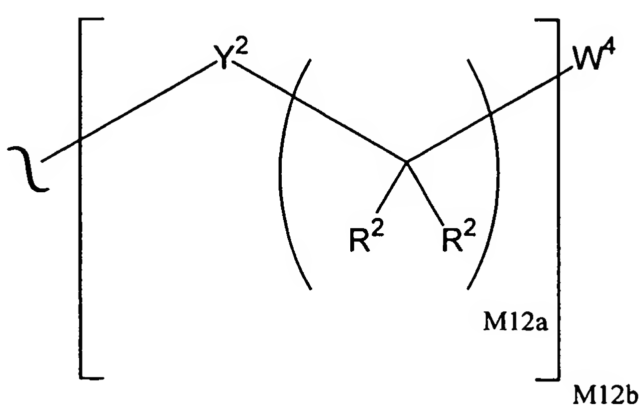
In an embodiment M12a is 1.

In an embodiment A^2 is selected from phenyl, substituted phenyl, benzyl, substituted benzyl, pyridyl and substituted pyridyl.

In an embodiment A^2 is of the formula:



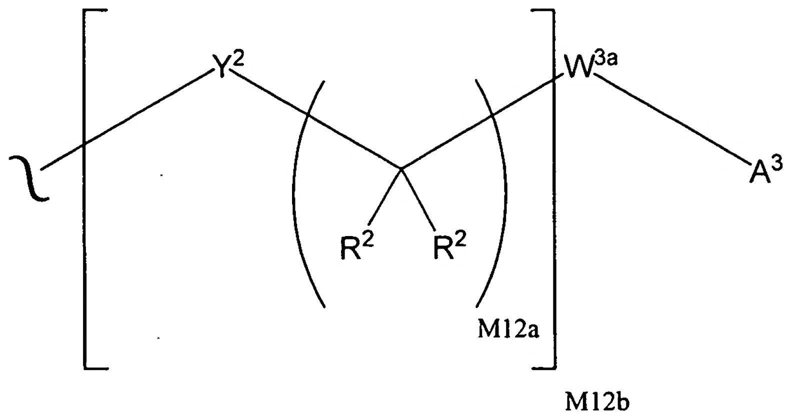
In an embodiment A^2 is of the formula:



.

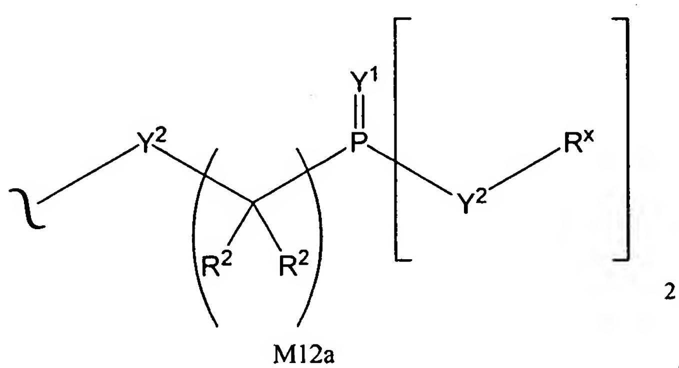
In an embodiment M12b is 1.

In an embodiment A^1 is of the formula:



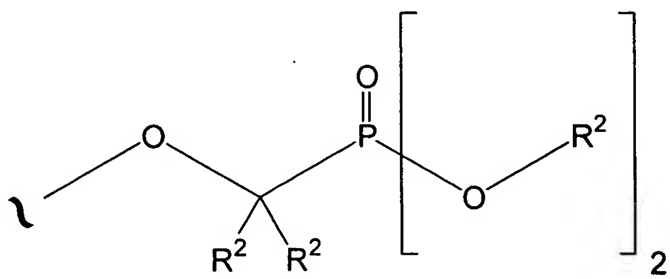
; and

A^3 is of the formula:



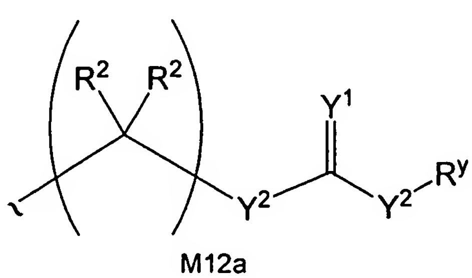
.

In an embodiment A^3 is of the formula:



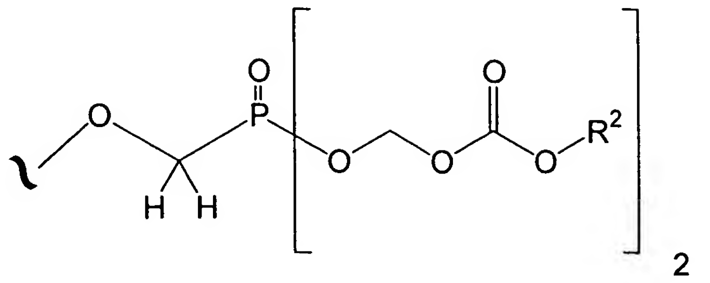
.

In an embodiment R^x is of the formula:

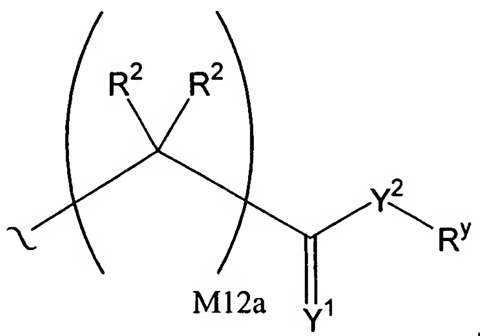


.

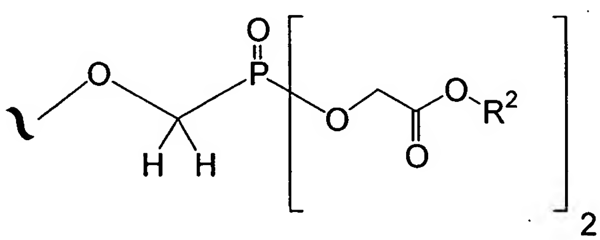
In an embodiment A^3 is of the formula:



In an embodiment R^x is of the formula:

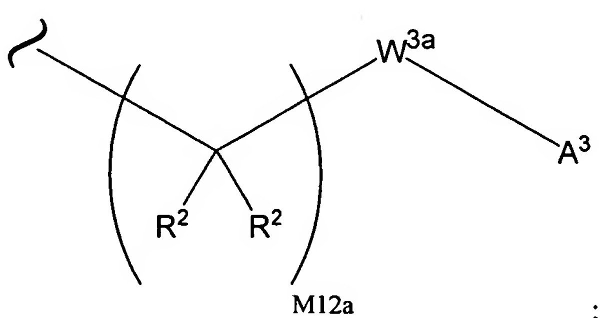


In an embodiment A^3 is of the formula:

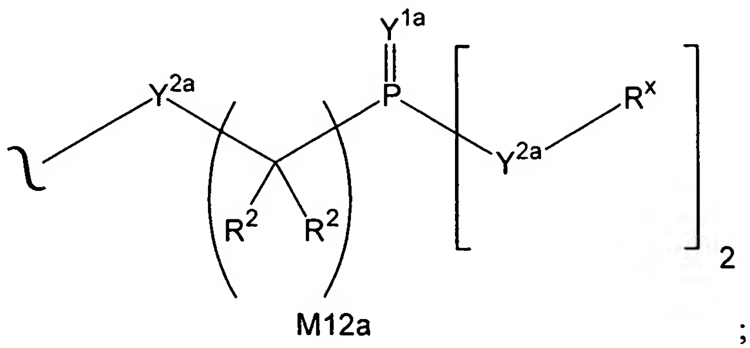


In an embodiment R^4 is isopropyl.

In an embodiment A^1 is of the formula:

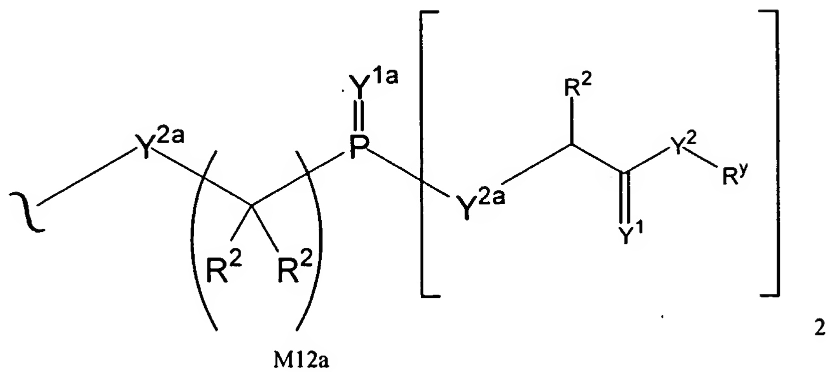


A^3 is of the formula:



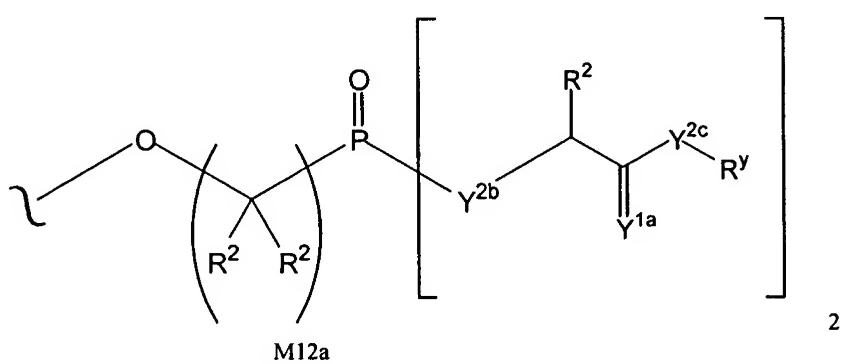
and Y^{1a} is O or S.

In an embodiment A^3 is of the formula:



and Y^{2a} is O, $N(R^2)$ or S.

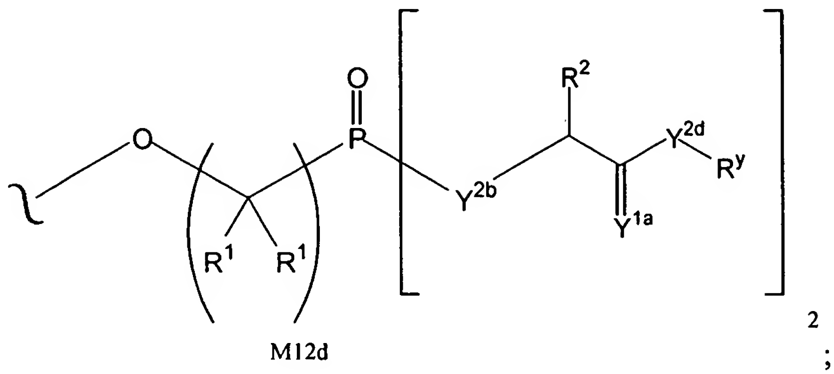
In an embodiment A^3 is of the formula:



Y^{2b} is O or $N(R^2)$; and

Y^{2c} is O, $N(R^y)$ or S.

In an embodiment A^3 is of the formula:



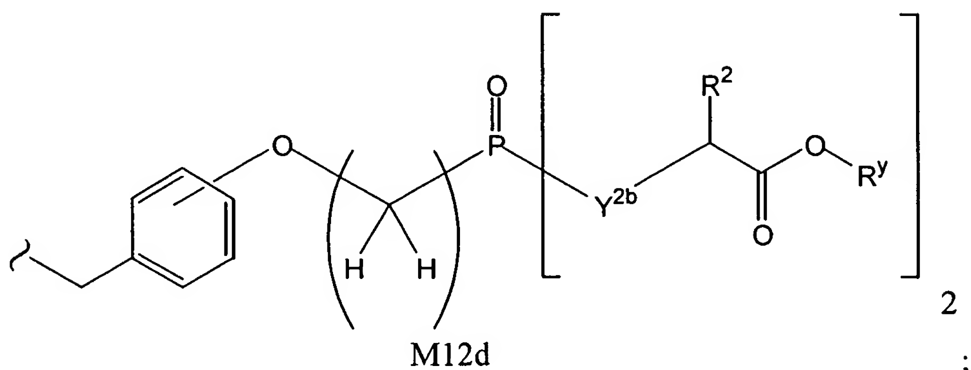
Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$;

Y^{2d} is O or $N(R^y)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

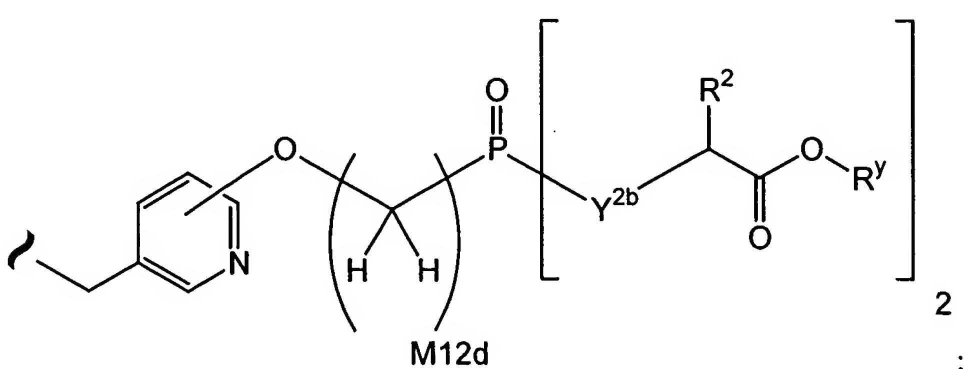
In an embodiment A^1 is of the formula:



Y^{2b} is O or $N(R^2)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

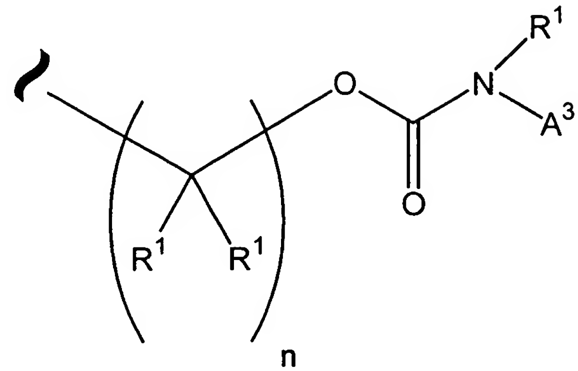
In an embodiment A^1 is of the formula:



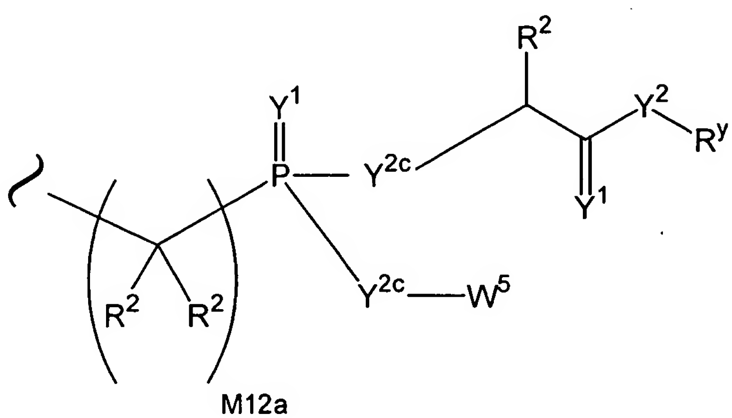
and Y^{2b} is O or $N(R^2)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In an embodiment A^1 is of the formula:



n is an integer from 1 to 18; A^3 is of the formula:

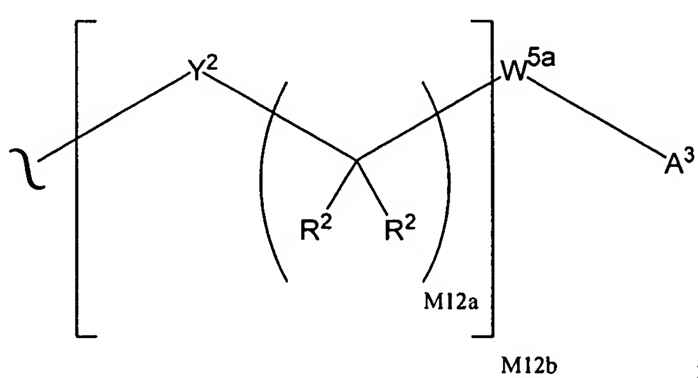


;

and Y^{2c} is O, $N(R^y)$ or S.

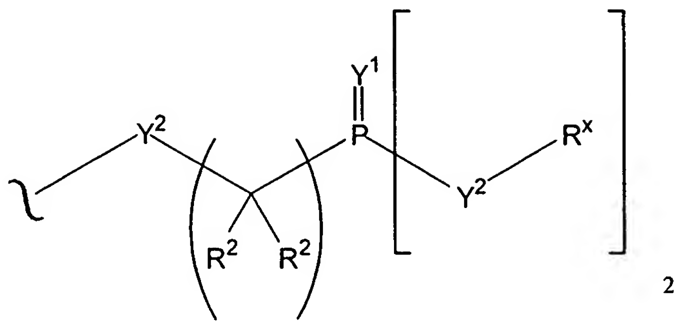
In an embodiment R^1 is H and n is 1.

In an embodiment A^1 is of the formula:



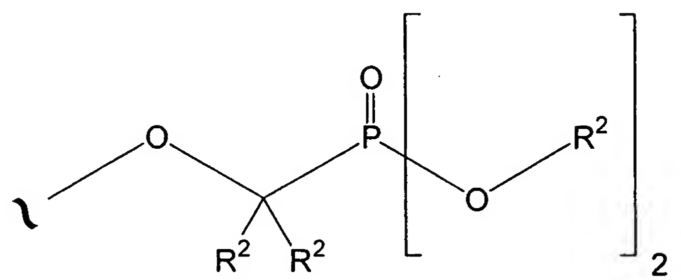
; and

A^3 is of the formula:

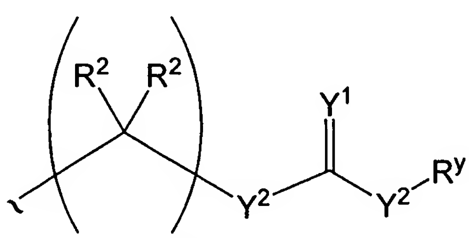


M12a

In an embodiment A^3 is of the formula:

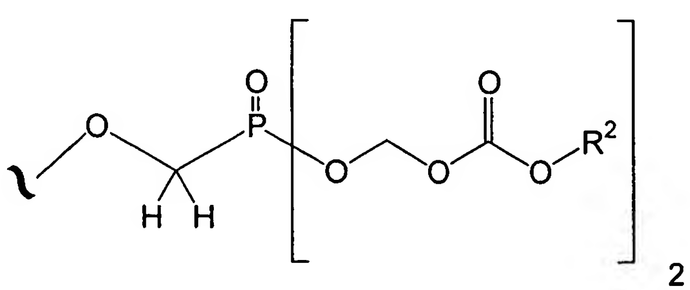


In an embodiment R^x is of the formula:

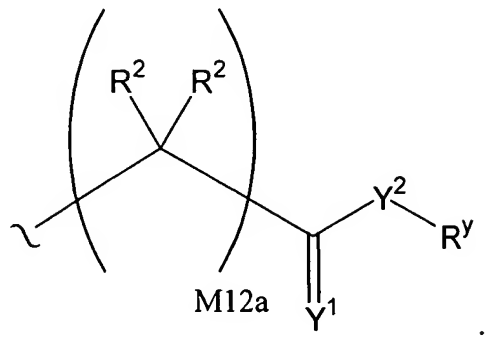


M12a

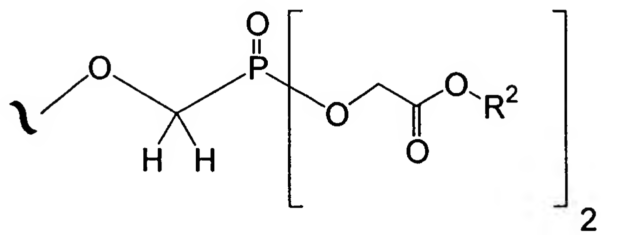
In an embodiment A^3 is of the formula:



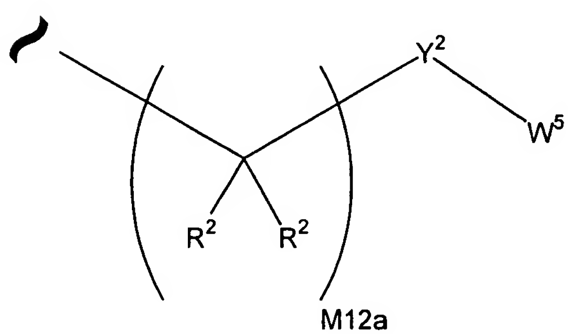
In an embodiment R^x is of the formula:



In an embodiment A^3 is of the formula:



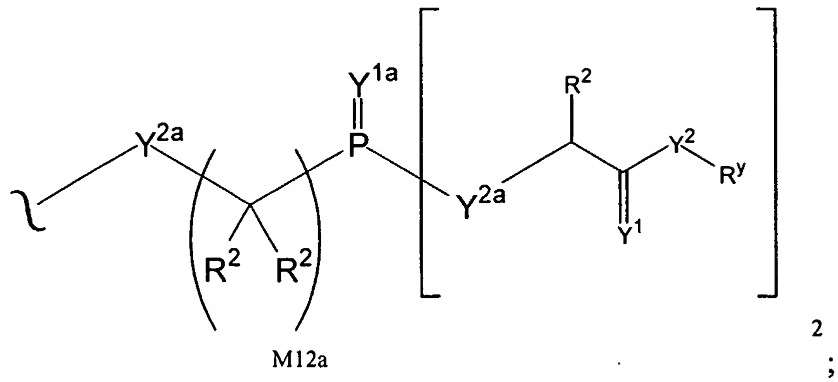
In an embodiment A^2 is selected from:



, Y^2–W^5 and W^5,

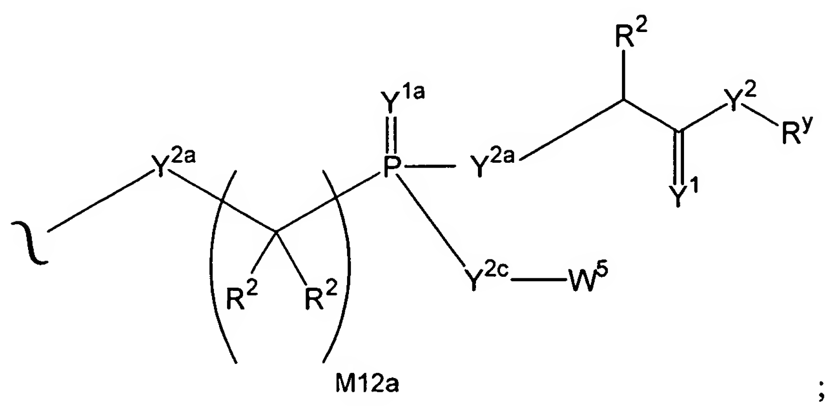
where W^5 is a carbocycle or a heterocycle and where W^5 is independently substituted with 0 to 3 R^2 groups.

In an embodiment A^3 is of the formula:



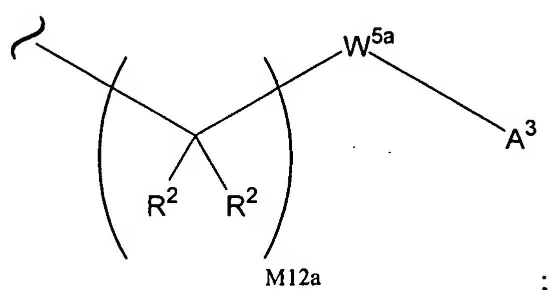
and Y^{2a} is O, N(R^2) or S.

In an embodiment A^3 is of the formula:

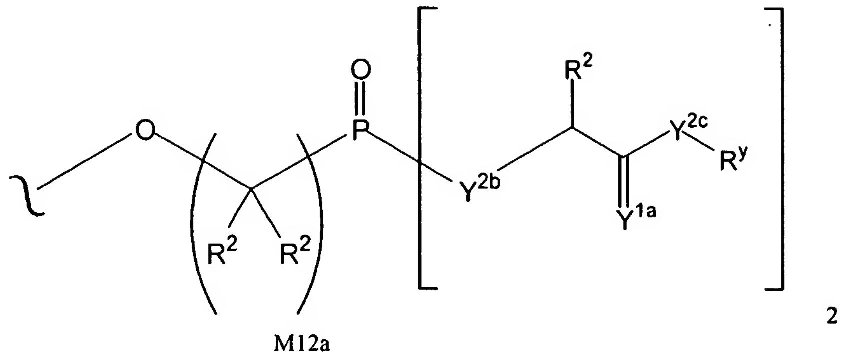


and Y^{2c} is O, N(R^y) or S.

In an embodiment A^1 is of the formula:



A^3 is of the formula:



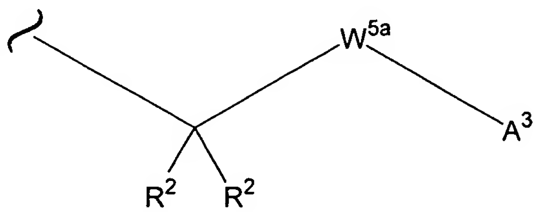
;

W^{5a} is a carbocycle or a heterocycle where the carbocycle or heterocycle is independently substituted with 0 to 3 R^2 groups;

Y^{2b} is O or $N(R^2)$; and

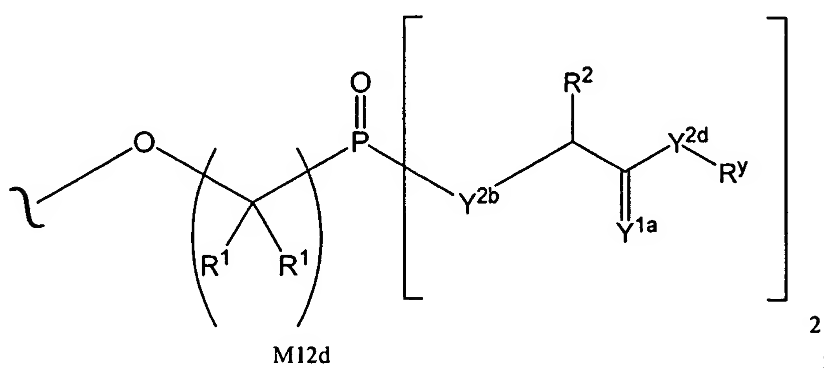
Y^{2c} is O, $N(R^y)$ or S.

In an embodiment A^1 is of the formula:



;

A^3 is of the formula:



;

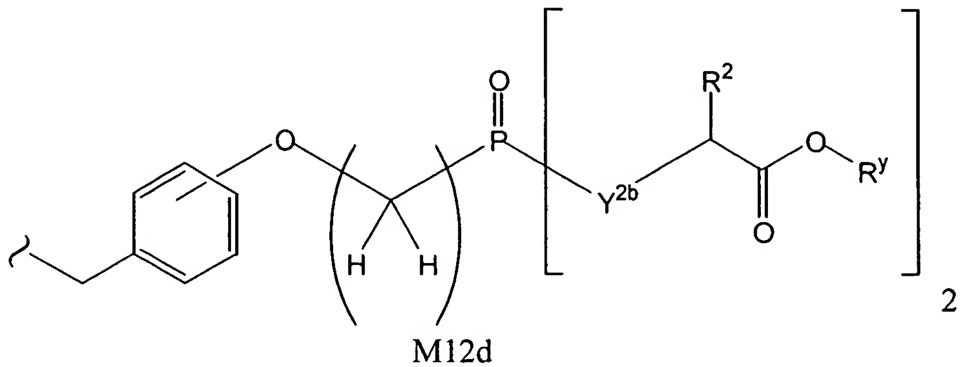
Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$;

Y^{2d} is O or $N(R^y)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In an embodiment A^1 is of the formula:

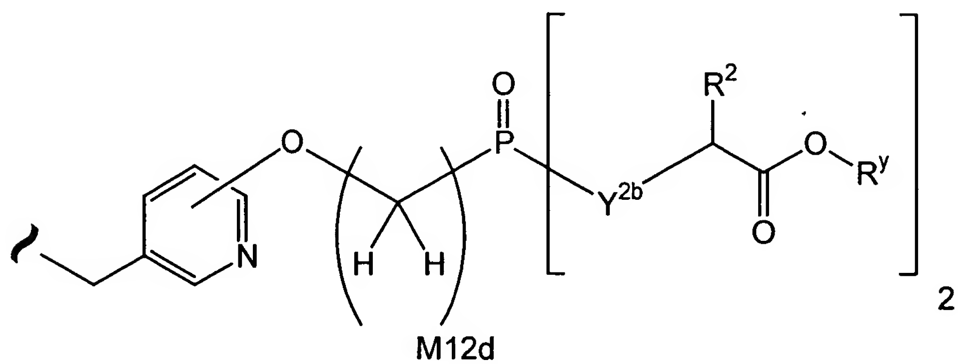


;

Y^{2b} is O or $N(R^2)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In an embodiment A^1 is of the formula:



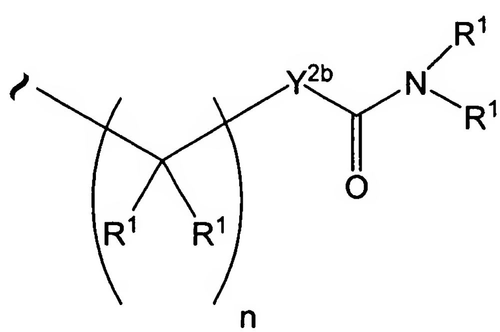
;

and Y^{2b} is O or $N(R^2)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In an embodiment A^2 is a phenyl substituted with 0 to 3 R^2 groups.

In an embodiment W^4 is of the formula:



wherein n is an integer from 1 to 18; and Y^{2b} is O or $N(R^2)$.

In an embodiment

A_1 is $-(X_2-(C(R_2)(R_2))_{m1}-X_3)_{m1}-W_3$, wherein W_3 is substituted with 1 to 3 A_3 groups;

A_2 is $-(X_2-(C(R_2)(R_2))_{m1}-X_3)_{m1}-W_3$;

A_3 is $-(X_2-(C(R_2)(R_2))_{m1}-X_3)_{m1}-P(Y_1)(Y_1R_{6a})(Y_1R_{6a})$;

X_2 and X_3 are independently a bond, -O-, $-N(R_2)-$, $-N(OR_2)-$, $-N(N(R_2)(R_2))-$, -S-, -SO-, or -SO2-;

each Y_1 is independently O, $N(R_2)$, $N(OR_2)$, or $N(N(R_2)(R_2))$, wherein each Y_1 is bound by two single bonds or one double bond;

R_1 is independently H or alkyl of 1 to 12 carbon atoms;

R_2 is independently H, R_1, R_3 or R_4 wherein each R_4 is independently substituted with 0 to 3 R_3 groups;

R_3 is independently F, Cl, Br, I, -CN, N_3, $-NO_2$, $-OR_{6a}$, $-OR_1$, $-N(R_1)_2$, $-N(R_1)(R_{6b})$, $-N(R_{6b})_2$, $-SR_1$, $-SR_{6a}$, $-S(O)R_1$, $-S(O)_2R_1$, $-S(O)OR_1$, $-S(O)OR_{6a}$, $-S(O)_2OR_1$, $-S(O)_2OR_{6a}$, $-C(O)OR_1$, $-C(O)R_{6c}$, $-C(O)OR_{6a}$, $-OC(O)R_1$, $-N(R_1)(C(O)R_1)$, $-N(R_{6b})(C(O)R_1)$, $-N(R_1)(C(O)OR_1)$, $-N(R_{6b})(C(O)OR_1)$, $-C(O)N(R_1)_2$, $-C(O)N(R_{6b})(R_1)$, $-C(O)N(R_{6b})_2$, $-C(NR_1)(N(R_1)_2)$, $-C(N(R_{6b}))(N(R_1)_2)$, $-C(N(R_1))(N(R_1)(R_{6b}))$, $-C(N(R_{6b}))(N(R_1)(R_{6b}))$, $-C(N(R_1))(N(R_{6b})_2)$, $-C(N(R_{6b}))(N(R_{6b})_2)$, $-N(R_1)C(N(R_1))(N(R_1)_2)$, $-N(R_1)C(N(R_1))(N(R_1)(R_{6b}))$, $-N(R_1)C(N(R_{6b}))(N(R_1)_2)$, $-N(R_{6b})C(N(R_1))(N(R_1)_2)$, $-N(R_{6b})C(N(R_{6b}))(N(R_1)_2)$, $-N(R_{6b})C(N(R_1))(N(R_1)(R_{6b}))$, $-N(R_1)C(N(R_{6b}))(N(R_1)(R_{6b}))$, $-N(R_1)C(N(R_1))(N(R_{6b})_2)$, $-N(R_{6b})C(N(R_{6b}))(N(R_1)(R_{6b}))$, $-N(R_{6b})C(N(R_1))(N(R_{6b})_2)$, $-N(R_1)C(N(R_{6b}))(N(R_{6b})_2)$, $-N(R_{6b})C(N(R_{6b}))(N(R_{6b})_2)$, =O, =S, $=N(R_1)$, $=N(R_{6b})$ or W_5;

R_4 is independently alkyl of 1 to 12 carbon atoms, alkenyl of 2 to 12 carbon atoms, or alkynyl of 2 to 12 carbon atoms;

R_5 is independently R_4 wherein each R_4 is substituted with 0 to 3 R_3 groups;

R_{5a} is independently alkylene of 1 to 12 carbon atoms, alkenylene of 2 to 12 carbon atoms, or alkynylene of 2-12 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R_3 groups;

R_{6a} is independently H or an ether- or ester-forming group;

R_{6b} is independently H, a protecting group for amino or the residue of a carboxyl-containing compound;

R_{6c} is independently H or the residue of an amino-containing compound;

W_3 is W_4 or W_5;

W_4 is R_5, $-C(Y_1)R_5$, $-C(Y_1)W_5$, $-SO_2R_5$, or $-SO_2W_5$;

W_5 is carbocycle or heterocycle wherein W_5 is independently substituted with 0 to 3 R_2 groups;

m1 is independently an integer from 0 to 12, wherein the sum of all m1's within each individual embodiment of A_1, A_2 or A_3 is 12 or less; and

m2 is independently an integer from 0 to 2.

In an embodiment

A_1 is $-(C(R_2)(R_2))_{m1}-W_3$, wherein W_3 is substituted with 1 A_3 group;

A_2 is $-(C(R_2)(R_2))_{m1}-W_3$; and

A_3 is $-(C(R_2)(R_2))_{m1}-P(Y_1)(Y_1R_{6a})(Y_1R_{6a})$.

Protecting Groups

The chemical substructure of a protecting group varies widely. One function of a protecting group is to serve as intermediates in the synthesis of the parental drug substance. Chemical protecting groups and strategies for protection/deprotection are well known in the art. See: Protective Groups in Organic Chemistry, Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991). Protecting groups are often utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, *e.g.*, making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of nal group, such as the polarity, lipophilicity (hydrophobicity), and other properties which can be measured by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive. Protected compounds may also exhibit altered, and in some cases, optimized properties *in vitro* and *in vivo*, such as passage through cellular membranes and resistance to enzymatic degradation or sequestration. In this role, protected compounds may in themselves exhibit therapeutic activity and need not be limited to the role of chemical intermediates or precursors. The protecting group need not be physiologically acceptable upon deprotection, although in general it is more desirable if such products are pharmacologically

innocuous.a compound alters other physical properties besides the reactivity of the protected function.

In the context of the present invention, embodiments of protecting groups include prodrug moieties and chemical protecting groups.

Protecting groups are available, commonly known and used, and are optionally used to prevent side reactions with the protected group during synthetic procedures, *i.e.* routes or methods to prepare the compounds of the invention. For the most part the decision as to which groups to protect, when to do so, and the nature of the chemical protecting group "PRT" will be dependent upon the chemistry of the reaction to be protected against (*e.g.*, acidic, basic, oxidative, reductive or other conditions) and the intended direction of the synthesis. The PRT groups do not need to be, and generally are not, the same if the compound is substituted with multiple PRT. In general, PRT will be used to protect functional groups such as carboxyl, hydroxyl or amino groups and to thus prevent side reactions or to otherwise facilitate the synthetic efficiency. The order of deprotection to yield free, deprotected groups is dependent upon the intended direction of the synthesis and the reaction conditions to be encountered, and may occur in any order as determined by the artisan.

Various functional groups of the compounds of the invention may be protection. For example, protecting groups for -OH groups (whether hydroxyl, carboxylic acid, phosphonic acid, or other functions) are embodiments of "ether- or ester-forming groups". Ether- or ester-forming groups are capable of functioning as chemical protecting groups in the synthetic schemes set forth herein. However, some hydroxyl and thio protecting groups are neither ether- nor ester-forming groups, as will be understood by those skilled in the art, and are included with amides, discussed below.

A very large number of hydroxyl protecting groups and amide-forming groups and corresponding chemical cleavage reactions are described in Protective Groups in Organic Chemistry, Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991, ISBN 0-471-62301-6) ("Greene"). See also Kocienski, Philip J.; Protecting Groups (Georg Thieme Verlag Stuttgart, New York, 1994), which is incorporated by reference in its entirety herein. In particular Chapter 1, Protecting Groups: An Overview, pages 1-20, Chapter 2, Hydroxyl Protecting Groups, pages 21-94, Chapter 3, Diol Protecting Groups, pages 95-117, Chapter 4, Carboxyl Protecting Groups, pages 118-154, Chapter 5, Carbonyl Protecting Groups, pages 155-

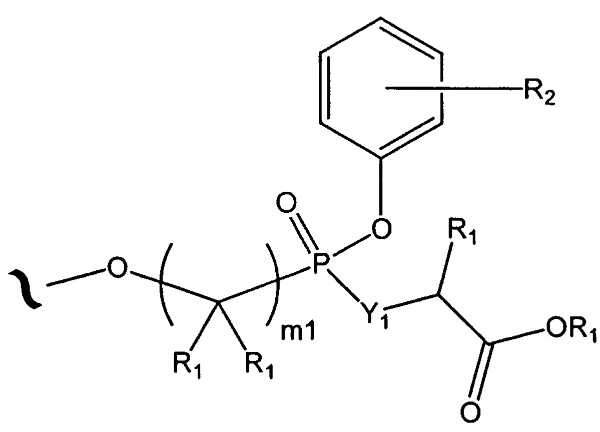
184. For protecting groups for carboxylic acid, phosphonic acid, phosphonate, sulfonic acid and other protecting groups for acids see Greene as set forth below. Such groups include by way of example and not limitation, esters, amides, hydrazides, and the like.

Ether- and Ester-forming protecting groups

Ester-forming groups include: (1) phosphonate ester-forming groups, such as phosphonamidate esters, phosphorothioate esters, phosphonate esters, and phosphon-bis-amidates; (2) carboxyl ester-forming groups, and (3) sulphur ester-forming groups, such as sulphonate, sulfate, and sulfinate.

The phosphonate moieties of the compounds of the invention may or may not be prodrug moieties, *i.e.* they may or may be susceptible to hydrolytic or enzymatic cleavage or modification. Certain phosphonate moieties are stable under most or nearly all metabolic conditions. For example, a dialkylphosphonate, where the alkyl groups are two or more carbons, may have appreciable stability *in vivo* due to a slow rate of hydrolysis.

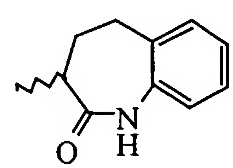
Within the context of phosphonate prodrug moieties, a large number of structurally-diverse prodrugs have been described for phosphonic acids (Freeman and Ross in Progress in Medicinal Chemistry 34: 112-147 (1997) and are included within the scope of the present invention. An exemplary embodiment of a phosphonate ester-forming group is the phenyl carbocycle in substructure A_3 having the formula:

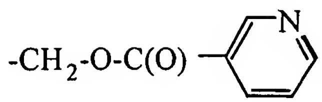
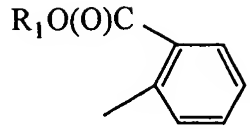
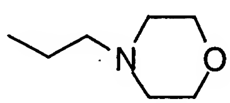


wherein m1 is 1, 2, 3, 4, 5, 6, 7 or 8, and the phenyl carbocycle is substituted with 0 to 3 R_2 groups. Also, in this embodiment, where Y_1 is O, a lactate ester is formed. Alternatively, where Y_1 is $N(R_2)$, $N(OR_2)$ or $N(N(R_2)_2)_2$, then phosphonamidate esters result. R_1 may be H or C_1–C_{12} alkyl.

In its ester-forming role, a protecting group typically is bound to any acidic group such as, by way of example and not limitation, a $-CO_2H$ or $-C(S)OH$ group, thereby resulting in $-CO_2R^x$ where R^x is defined herein. Also, R^x for example includes the enumerated ester groups of WO 95/07920.

Examples of protecting groups include:

C_3-C_{12} heterocycle (described above) or aryl. These aromatic groups optionally are polycyclic or monocyclic. Examples include phenyl, spiryl, 2- and 3-pyrrolyl, 2- and 3-thienyl, 2- and 4-imidazolyl, 2-, 4- and 5-oxazolyl, 3- and 4-isoxazolyl, 2-, 4- and 5-thiazolyl, 3-, 4- and 5-isothiazolyl, 3- and 4-pyrazolyl, 1-, 2-, 3- and 4-pyridinyl, and 1-, 2-, 4- and 5-pyrimidinyl, C_3-C_{12} heterocycle or aryl substituted with halo, R^1, R^1-O-C_1-C_{12} alkylene, C_1-C_{12} alkoxy, CN, NO_2, OH, carboxy, carboxyester, thiol, thioester, C_1-C_{12} haloalkyl (1-6 halogen atoms), C_2-C_{12} alkenyl or C_2-C_{12} alkynyl. Such groups include 2-, 3- and 4-alkoxyphenyl (C_1-C_{12} alkyl), 2-, 3- and 4-methoxyphenyl, 2-, 3- and 4-ethoxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-diethoxyphenyl, 2- and 3-carboethoxy-4-hydroxyphenyl, 2- and 3-ethoxy-4-hydroxyphenyl, 2- and 3-ethoxy-5-hydroxyphenyl, 2- and 3-ethoxy-6-hydroxyphenyl, 2-, 3- and 4-O-acetylphenyl, 2-, 3- and 4-dimethylaminophenyl, 2-, 3- and 4-methylmercaptophenyl, 2-, 3- and 4-halophenyl (including 2-, 3- and 4-fluorophenyl and 2-, 3- and 4-chlorophenyl), 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-biscarboxyethylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethoxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dihalophenyl (including 2,4-difluorophenyl and 3,5-difluorophenyl), 2-, 3- and 4-haloalkylphenyl (1 to 5 halogen atoms, C_1-C_{12} alkyl including 4-trifluoromethylphenyl), 2-, 3- and 4-cyanophenyl, 2-, 3- and 4-nitrophenyl, 2-, 3- and 4-haloalkylbenzyl (1 to 5 halogen atoms, C_1-C_{12} alkyl including 4-trifluoromethylbenzyl and 2-, 3- and 4-trichloromethylphenyl and 2-, 3- and 4-trichloromethylphenyl), 4-N-methylpiperidinyl, 3-N-methylpiperidinyl, 1-ethylpiperazinyl, benzyl, alkylsalicylphenyl (C_1-C_4 alkyl, including 2-, 3- and 4-ethylsalicylphenyl), 2-,3- and 4-acetylphenyl, 1,8-dihydroxynaphthyl ($-C_{10}H_6$-OH) and aryloxy ethyl [C_6-C_9 aryl (including phenoxy ethyl)], 2,2'-dihydroxybiphenyl, 2-, 3- and 4-N,N-dialkylaminophenol, $-C_6H_4CH_2$-$N(CH_3)_2$, trimethoxybenzyl, triethoxybenzyl, 2-alkyl pyridinyl (C_{1-4} alkyl);  ;

 ;  ; C_4 - C_8 esters of 2-carboxyphenyl; and C_1-C_4 alkylene-C_3-C_6 aryl (including benzyl, -CH_2-pyrrolyl, -CH_2-thienyl, -CH_2-imidazolyl, -CH_2-oxazolyl, -CH_2-isoxazolyl, -CH_2-thiazolyl, -CH_2-isothiazolyl, -CH_2-pyrazolyl, -CH_2-pyridinyl and -CH_2-pyrimidinyl) substituted in the aryl moiety by 3 to 5 halogen atoms or 1 to 2 atoms or groups selected from halogen, C_1-C_{12} alkoxy (including methoxy and ethoxy), cyano, nitro, OH, C_1-C_{12} haloalkyl (1 to 6 halogen atoms; including -CH_2CCl_3), C_1-C_{12} alkyl (including methyl and ethyl), C_2-C_{12} alkenyl or C_2-C_{12} alkynyl; alkoxy ethyl [C_1-C_6 alkyl including -CH_2-CH_2-O-CH_3 (methoxy ethyl)]; alkyl substituted by any of the groups set forth above for aryl, in particular OH or by 1 to 3 halo atoms (including -CH_3, -$CH(CH_3)_2$, -$C(CH_3)_3$, -CH_2CH_3, -$(CH_2)_2CH_3$, -$(CH_2)_3CH_3$, -$(CH_2)_4CH_3$, -$(CH_2)_5CH_3$, -CH_2CH_2F, -CH_2CH_2Cl, -CH_2CF_3, and -CH_2CCl_3);  ; -N-2-propylmorpholino, 2,3-dihydro-6-hydroxyindene, sesamol, catechol monoester, -CH_2-C(O)-N(R^1)$_2$, -CH_2-S(O)(R^1), -CH_2-S(O)$_2$(R^1), -CH_2-CH(OC(O)CH_2R^1)-CH_2(OC(O)CH_2R^1), cholesteryl, enolpyruvate (HOOC-C(=CH_2)-), glycerol;

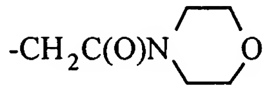
a 5 or 6 carbon monosaccharide, disaccharide or oligosaccharide (3 to 9 monosaccharide residues);

triglycerides such as α-D-β-diglycerides (wherein the fatty acids composing glyceride lipids generally are naturally occurring saturated or unsaturated C_{6-26}, C_{6-18} or C_{6-10} fatty acids such as linoleic, lauric, myristic, palmitic, stearic, oleic, palmitoleic, linolenic and the like fatty acids) linked to acyl of the parental compounds herein through a glyceryl oxygen of the triglyceride;

phospholipids linked to the carboxyl group through the phosphate of the phospholipid;

phthalidyl (shown in Fig. 1 of Clayton *et al.*, *Antimicrob. Agents Chemo.* (1974) 5(6):670-671;

cyclic carbonates such as (5-R_d-2-oxo-1,3-dioxolen-4-yl) methyl esters (Sakamoto *et al.*, *Chem. Pharm. Bull.* (1984) 32(6)2241-2248) where R_d is R_1, R_4 or aryl; and

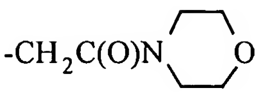

;

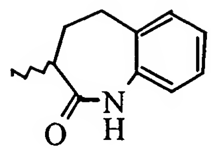
The hydroxyl groups of the compounds of this invention optionally are substituted with one of groups III, IV or V disclosed in WO 94/21604, or with isopropyl.

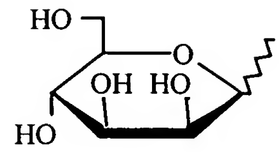
As further embodiments, Table A lists examples of protecting group ester moieties that for example can be bonded via oxygen to -C(O)O- and $-P(O)(O-)_2$ groups. Several amidates also are shown, which are bound directly to -C(O)- or $-P(O)_2$. Esters of structures 1-5, 8-10 and 16, 17, 19-22 are synthesized by reacting the compound herein having a free hydroxyl with the corresponding halide (chloride or acyl chloride and the like) and N ,N-dicyclohexyl-N-morpholine carboxamidine (or another base such as DBU, triethylamine, $CsCO_3$, N,N-dimethylaniline and the like) in DMF (or other solvent such as acetonitrile or N-methylpyrrolidone). When the compound to be protected is a phosphonate, the esters of structures 5-7, 11, 12, 21, and 23-26 are synthesized by reaction of the alcohol or alkoxide salt (or the corresponding amines in the case of compounds such as 13, 14 and 15) with the monochlorophosphonate or dichlorophosphonate (or another activated phosphonate).

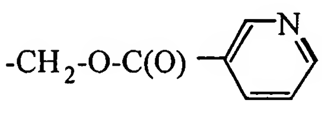
TABLE A

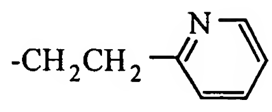
1. $-CH_2-C(O)-N(R_1)_2$ *	10. $-CH_2-O-C(O)-C(CH_3)_3$
2. $-CH_2-S(O)(R_1)$	11. $-CH_2-CCl_3$
3. $-CH_2-S(O)_2(R_1)$	12. $-C_6H_5$
4. $-CH_2-O-C(O)-CH_2-C_6H_5$	13. $-NH-CH_2-C(O)O-CH_2CH_3$
5. 3-cholesteryl	14. $-N(CH_3)-CH_2-C(O)O-CH_2CH_3$
6. 3-pyridyl	15. $-NHR_1$
7. N-ethylmorpholino	16. $-CH_2-O-C(O)-C_{10}H_{15}$
8. $-CH_2-O-C(O)-C_6H_5$	17. $-CH_2-O-C(O)-CH(CH_3)_2$
9. $-CH_2-O-C(O)-CH_2CH_3$	18. $-CH_2-C\#H(OC(O)CH_2R_1)-CH_2-$ $-(OC(O)CH_2R_1)$*

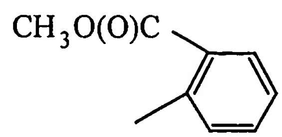
19. 

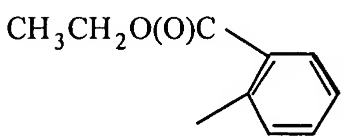
20. 

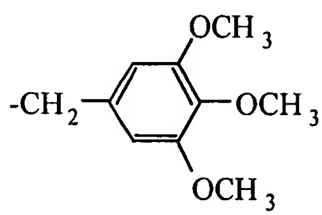
21. 

22. 

23. 

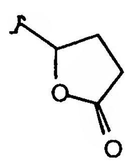
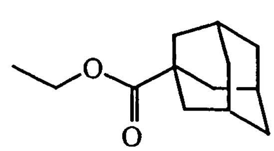
24. 

25. 

26. 

- chiral center is (R), (S) or racemate.

Other esters that are suitable for use herein are described in EP 632048.

Protecting groups also include "double ester" forming profunctionalities such as -$CH_2OC(O)OCH_3$,  -CH_2SCOCH_3, -$CH_2OCON(CH_3)_2$, or alkyl- or aryl-acyloxyalkyl groups of the structure -$CH(R^1$ or $W^5)O((CO)R^{37})$ or -$CH(R^1$ or $W^5)((CO)OR^{38})$ (linked to oxygen of the acidic group) wherein R^{37} and R^{38} are alkyl, aryl, or alkylaryl groups (see U.S. patent 4,968,788). Frequently R^{37} and R^{38} are bulky groups such as branched alkyl, ortho-substituted aryl, meta-substituted aryl, or combinations thereof, including normal, secondary, iso- and tertiary alkyls of 1-6 carbon atoms. An example is the pivaloyloxymethyl group. These are of particular use with prodrugs for oral administration. Examples of such useful protecting groups are alkylacyloxymethyl esters and their derivatives, including -$CH(CH_2CH_2OCH_3)OC(O)C(CH_3)_3$,  ; -$CH_2OC(O)C_{10}H_{15}$, -$CH_2OC(O)C(CH_3)_3$, -$CH(CH_2OCH_3)OC(O)C(CH_3)_3$, -$CH(CH(CH_3)_2)OC(O)C(CH_3)_3$,

$-CH_2OC(O)CH_2CH(CH_3)_2$, $-CH_2OC(O)C_6H_{11}$, $-CH_2OC(O)C_6H_5$, $-CH_2OC(O)C_{10}H_{15}$, $-CH_2OC(O)CH_2CH_3$, $-CH_2OC(O)CH(CH_3)_2$, $-CH_2OC(O)C(CH_3)_3$ and $-CH_2OC(O)CH_2C_6H_5$.

For prodrug purposes, the ester typically chosen is one heretofore used for antibiotic drugs, in particular the cyclic carbonates, double esters, or the phthalidyl, aryl or alkyl esters.

In some embodiments the protected acidic group is an ester of the acidic group and is the residue of a hydroxyl-containing functionality. In other embodiments, an amino compound is used to protect the acid functionality. The residues of suitable hydroxyl or amino-containing functionalities are set forth above or are found in WO 95/07920. Of particular interest are the residues of amino acids, amino acid esters, polypeptides, or aryl alcohols. Typical amino acid, polypeptide and carboxyl-esterified amino acid residues are described on pages 11-18 and related text of WO 95/07920 as groups L1 or L2. WO 95/07920 expressly teaches the amidates of phosphonic acids, but it will be understood that such amidates are formed with any of the acid groups set forth herein and the amino acid residues set forth in WO 95/07920.

Typical esters for protecting acidic functionalities are also described in WO 95/07920, again understanding that the same esters can be formed with the acidic groups herein as with the phosphonate of the '920 publication. Typical ester groups are defined at least on WO 95/07920 pages 89-93 (under R^{31} or R^{35}), the table on page 105, and pages 21-23 (as R). Of particular interest are esters of unsubstituted aryl such as phenyl or arylalkyl such benzyl, or hydroxy-, halo-, alkoxy-, carboxy- and/or alkylestercarboxy-substituted aryl or alkylaryl, especially phenyl, ortho-ethoxyphenyl, or C_1-C_4 alkylestercarboxyphenyl (salicylate C_1-C_{12} alkylesters).

The protected acidic groups, particularly when using the esters or amides of WO 95/07920, are useful as prodrugs for oral administration. However, it is not essential that the acidic group be protected in order for the compounds of this invention to be effectively administered by the oral route. When the compounds of the invention having protected groups, in particular amino acid amidates or substituted and unsubstituted aryl esters are administered systemically or orally they are capable of hydrolytic cleavage *in vivo* to yield the free acid.

One or more of the acidic hydroxyls are protected. If more than one acidic hydroxyl is protected then the same or a different protecting group is employed, *e.g.*, the esters may be different or the same, or a mixed amidate and ester may be used.

Typical hydroxy protecting groups described in Greene (pages 14-118) include substituted methyl and alkyl ethers, substituted benzyl ethers, silyl ethers, esters including sulfonic acid esters, and carbonates. For example:

- Ethers (methyl, *t*-butyl, allyl);
- Substituted Methyl Ethers (Methoxymethyl, Methylthiomethyl, *t*-Butylthiomethyl, (Phenyldimethylsilyl)methoxymethyl, Benzyloxymethyl, *p*-Methoxybenzyloxymethyl, (4-Methoxyphenoxy)methyl, Guaiacolmethyl, *t*-Butoxymethyl, 4-Pentenyloxymethyl, Siloxymethyl, 2-Methoxyethoxymethyl, 2,2,2-Trichloroethoxymethyl, Bis(2-chloroethoxy)methyl, 2-(Trimethylsilyl)ethoxymethyl, Tetrahydropyranyl, 3-Bromotetrahydropyranyl, Tetrahydropthiopyranyl, 1-Methoxycyclohexyl, 4-Methoxytetrahydropyranyl, 4-Methoxytetrahydrothiopyranyl, 4-Methoxytetrahydropthiopyranyl *S,S*-Dioxido, 1-[(2-Chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1,4-Dioxan-2-yl, Tetrahydrofuranyl, Tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl));
- Substituted Ethyl Ethers (1-Ethoxyethyl, 1-(2-Chloroethoxy)ethyl, 1-Methyl-1-methoxyethyl, 1-Methyl-1-benzyloxyethyl, 1-Methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-Trichloroethyl, 2-Trimethylsilylethyl, 2-(Phenylselenyl)ethyl,
- *p*-Chlorophenyl, *p*-Methoxyphenyl, 2,4-Dinitrophenyl, Benzyl);
- Substituted Benzyl Ethers (*p*-Methoxybenzyl, 3,4-Dimethoxybenzyl, *o*-Nitrobenzyl, *p*-Nitrobenzyl, *p*-Halobenzyl, 2,6-Dichlorobenzyl, *p*-Cyanobenzyl, *p*-Phenylbenzyl, 2- and 4-Picolyl, 3-Methyl-2-picolyl *N*-Oxido, Diphenylmethyl, *p,p'*-Dinitrobenzhydryl, 5-Dibenzosuberyl, Triphenylmethyl, α-Naphthyldiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, Di(*p*-methoxyphenyl)phenylmethyl, Tri(*p*-methoxyphenyl)methyl, 4-(4'-Bromophenacyloxy)phenyldiphenylmethyl, 4,4',4"-Tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4"-Tris(levulinoyloxyphenyl)methyl, 4,4',4"-Tris(benzoyloxyphenyl)methyl, 3-(Imidazol-1-ylmethyl)bis(4',4"-dimethoxyphenyl)methyl, 1,1-Bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-Anthryl, 9-(9-Phenyl)xanthenyl, 9-(9-Phenyl-10-oxo)anthryl, 1,3-Benzodithiolan-2-yl, Benzisothiazolyl *S,S*-Dioxido);
- Silyl Ethers (Trimethylsilyl, Triethylsilyl, Triisopropylsilyl, Dimethylisopropylsilyl, Diethylisopropylsilyl, Dimethylthexylsilyl, *t*-Butyldimethylsilyl, *t*-Butyldiphenylsilyl, Tribenzylsilyl, Tri-*p*-xylylsilyl, Triphenylsilyl, Diphenylmethylsilyl, *t*-

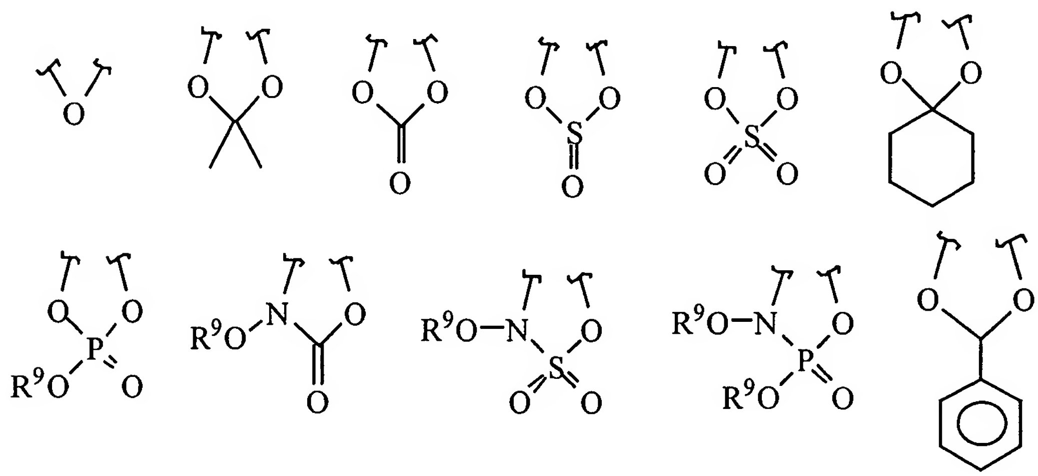
Butylmethoxyphenylsilyl);

- Esters (Formate, Benzoylformate, Acetate, Choroacetate, Dichloroacetate, Trichloroacetate, Trifluoroacetate, Methoxyacetate, Triphenylmethoxyacetate, Phenoxyacetate, *p*-Chlorophenoxyacetate, *p*-poly-Phenylacetate, 3-Phenylpropionate, 4-Oxopentanoate (Levulinate), 4,4-(Ethylenedithio)pentanoate, Pivaloate, Adamantoate, Crotonate, 4-Methoxycrotonate, Benzoate, *p*-Phenylbenzoate, 2,4,6-Trimethylbenzoate (Mesitoate));
- Carbonates (Methyl, 9-Fluorenylmethyl, Ethyl, 2,2,2-Trichloroethyl, 2-(Trimethylsilyl)ethyl, 2-(Phenylsulfonyl)ethyl, 2-(Triphenylphosphonio)ethyl, Isobutyl, Vinyl, Allyl, *p*-Nitrophenyl, Benzyl, *p*-Methoxybenzyl, 3,4-Dimethoxybenzyl, *o*-Nitrobenzyl, *p*-Nitrobenzyl, *S*-Benzyl Thiocarbonate, 4-Ethoxy-1-naphthyl, Methyl Dithiocarbonate);
- Groups With Assisted Cleavage (2-Iodobenzoate, 4-Azidobutyrate, 4-Nitro-4-methylpentanoate, *o*-(Dibromomethyl)benzoate, 2-Formylbenzenesulfonate, 2-(Methylthiomethoxy)ethyl Carbonate, 4-(Methylthiomethoxy)butyrate, 2-(Methylthiomethoxymethyl)benzoate); Miscellaneous Esters (2,6-Dichloro-4-methylphenoxyacetate, 2,6-Dichloro-4-(1,1,3,3 tetramethylbutyl)phenoxyacetate, 2,4-Bis(1,1-dimethylpropyl)phenoxyacetate, Chlorodiphenylacetate, Isobutyrate, Monosuccinate, (*E*)-2-Methyl-2-butenoate (Tigloate), *o*-(Methoxycarbonyl)benzoate, *p*-poly-Benzoate, α-Naphthoate, Nitrate, Alkyl *N,N,N',N'*-Tetramethylphosphorodiamidate, *N*-Phenylcarbamate, Borate, Dimethylphosphinothioyl, 2,4-Dinitrophenylsulfenate); and
- Sulfonates (Sulfate, Methanesulfonate (Mesylate), Benzylsulfonate, Tosylate).
- Typical 1,2-diol protecting groups (thus, generally where two OH groups are taken together with the protecting functionality) are described in Greene at pages 118-142 and include Cyclic Acetals and Ketals (Methylene, Ethylidene, 1-*t*-Butylethylidene, 1-Phenylethylidene, (4-Methoxyphenyl)ethylidene, 2,2,2-Trichloroethylidene, Acetonide (Isopropylidene), Cyclopentylidene, Cyclohexylidene, Cycloheptylidene, Benzylidene, *p*-Methoxybenzylidene, 2,4-Dimethoxybenzylidene, 3,4-Dimethoxybenzylidene, 2-Nitrobenzylidene); Cyclic Ortho Esters (Methoxymethylene, Ethoxymethylene, Dimethoxymethylene, 1-Methoxyethylidene, 1-Ethoxyethylidine, 1,2-Dimethoxyethylidene, α-Methoxybenzylidene, 1-(*N,N*-Dimethylamino)ethylidene Derivative, α -(*N,N*-Dimethylamino)benzylidene Derivative, 2-Oxacyclopentylidene); Silyl Derivatives (Di-*t*-butylsilylene Group, 1,3-(1,1,3,3-Tetraisopropyldisiloxanylidene), and Tetra-*t*-butoxydisiloxane-1,3-diylidene), Cyclic

Carbonates, Cyclic Boronates, Ethyl Boronate and Phenyl Boronate.

More typically, 1,2-diol protecting groups include those shown in Table B, still more typically, epoxides, acetonides, cyclic ketals and aryl acetals.

Table B



wherein R^9 is C_1-C_6 alkyl.

<u>Amino protecting groups</u>

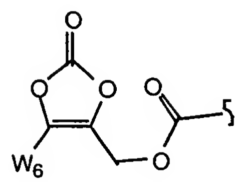
Another set of protecting groups include any of the typical amino protecting groups described by Greene at pages 315-385. They include:

- Carbamates: (methyl and ethyl, 9-fluorenylmethyl, 9(2-sulfo)fluorenylmethyl, 9-(2,7-dibromo)fluorenylmethyl, 2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl, 4-methoxyphenacyl);
- Substituted Ethyl: (2,2,2-trichoroethyl, 2-trimethylsilylethyl, 2-phenylethyl, 1-(1-adamantyl)-1-methylethyl, 1,1-dimethyl-2-haloethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 1-methyl-1-(4-biphenylyl)ethyl, 1-(3,5-di-*t*-butylphenyl)-1-methylethyl, 2-(2'- and 4'-pyridyl)ethyl, 2-(*N,N*-dicyclohexylcarboxamido)ethyl, *t*-butyl, 1-adamantyl, vinyl, allyl, 1-isopropylallyl, cinnamyl, 4-nitrocinnamyl, 8-quinolyl, *N*-hydroxypiperidinyl, alkyldithio, benzyl, *p*-methoxybenzyl, *p*-nitrobenzyl, *p*-bromobenzyl, *p*-chlorobenzyl, 2,4-dichlorobenzyl, 4-methylsulfinylbenzyl, 9-anthrylmethyl, diphenylmethyl);

- Groups With Assisted Cleavage: (2-methylthioethyl, 2-methylsulfonylethyl, 2-(*p*-toluenesulfonyl)ethyl, [2-(1,3-dithianyl)]methyl, 4-methylthiophenyl, 2,4-dimethylthiophenyl, 2-phosphonioethyl, 2-triphenylphosphonioisopropyl, 1,1-dimethyl-2-cyanoethyl, *m*-choro-*p*-acyloxybenzyl, *p*-(dihydroxyboryl)benzyl, 5-benzisoxazolylmethyl, 2-(trifluoromethyl)-6-chromonylmethyl);
- Groups Capable of Photolytic Cleavage: (*m*-nitrophenyl, 3,5-dimethoxybenzyl, *o*-nitrobenzyl, 3,4-dimethoxy-6-nitrobenzyl, phenyl(*o*-nitrophenyl)methyl); Urea-Type Derivatives (phenothiazinyl-(10)-carbonyl, *N'*-*p*-toluenesulfonylaminocarbonyl, *N'*-phenylaminothiocarbonyl);
- Miscellaneous Carbamates: (*t*-amyl, *S*-benzyl thiocarbamate, *p*-cyanobenzyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopropylmethyl, *p*-decyloxybenzyl, diisopropylmethyl, 2,2-dimethoxycarbonylvinyl, *o*-(*N,N*-dimethylcarboxamido)benzyl, 1,1-dimethyl-3-(*N,N*-dimethylcarboxamido)propyl, 1,1-dimethylpropynyl, di(2-pyridyl)methyl, 2-furanylmethyl, 2-Iodoethyl, Isobornyl, Isobutyl, Isonicotinyl, *p*-(*p*'-Methoxyphenylazo)benzyl, 1-methylcyclobutyl, 1-methylcyclohexyl, 1-methyl-1-cyclopropylmethyl, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl, 1-methyl-1-(*p*-phenylazophenyl)ethyl, 1-methyl-1-phenylethyl, 1-methyl-1-(4-pyridyl)ethyl, phenyl, *p*-(phenylazo)benzyl, 2,4,6-tri-*t*-butylphenyl, 4-(trimethylammonium)benzyl, 2,4,6-trimethylbenzyl);
- Amides: (*N*-formyl, *N*-acetyl, *N*-choroacetyl, *N*-trichoroacetyl, *N*-trifluoroacetyl, *N*-phenylacetyl, *N*-3-phenylpropionyl, *N*-picolinoyl, *N*-3-pyridylcarboxamide, *N*-benzoylphenylalanyl, *N*-benzoyl, *N*-*p*-phenylbenzoyl);
- Amides With Assisted Cleavage: (*N*-*o*-nitrophenylacetyl, *N*-*o*-nitrophenoxyacetyl, *N*-acetoacetyl, (*N'*-dithiobenzyloxycarbonylamino)acetyl, *N*-3-(*p*-hydroxyphenyl)propionyl, *N*-3-(*o*-nitrophenyl)propionyl, *N*-2-methyl-2-(*o*-nitrophenoxy)propionyl, *N*-2-methyl-2-(*o*-phenylazophenoxy)propionyl, *N*-4-chlorobutyryl, *N*-3-methyl-3-nitrobutyryl, *N*-*o*-nitrocinnamoyl, *N*-acetylmethionine, *N*-*o*-nitrobenzoyl, *N*-*o*-(benzoyloxymethyl)benzoyl, 4,5-diphenyl-3-oxazolin-2-one);
- Cyclic Imide Derivatives: (*N*-phthalimide, *N*-dithiasuccinoyl, *N*-2,3-diphenylmaleoyl, *N*-2,5-dimethylpyrrolyl, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct, 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3-5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridonyl);

- *N*-Alkyl and *N*-Aryl Amines: (*N*-methyl, *N*-allyl, *N*-[2-(trimethylsilyl)ethoxy]methyl, *N*-3-acetoxypropyl, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl), Quaternary Ammonium Salts, *N*-benzyl, *N*-di(4-methoxyphenyl)methyl, *N*-5-dibenzosuberyl, *N*-triphenylmethyl, *N*-(4-methoxyphenyl)diphenylmethyl, *N*-9-phenylfluorenyl, *N*-2,7-dichloro-9-fluorenylmethylene, *N*-ferrocenylmethyl, *N*-2-picolylamine *N'*-oxide);
- Imine Derivatives: (*N*-1,1-dimethylthiomethylene, *N*-benzylidene, *N*-*p*-methoxybenylidene, *N*-diphenylmethylene, *N*-[(2-pyridyl)mesityl]methylene, *N*,(*N'*,*N'*-dimethylaminomethylene, *N*,*N'*-isopropylidene, *N*-*p*-nitrobenzylidene, *N*-salicylidene, *N*-5-chlorosalicylidene, *N*-(5-chloro-2-hydroxyphenyl)phenylmethylene, *N*-cyclohexylidene);
- Enamine Derivatives: (*N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl));
- *N*-Metal Derivatives (*N*-borane derivatives, *N*-diphenylborinic acid derivatives, *N*-[phenyl(pentacarbonylchromium- or -tungsten)]carbenyl, *N*-copper or *N*-zinc chelate);
- N-N Derivatives: (*N*-nitro, *N*-nitroso, *N*-oxide);
- N-P Derivatives: (*N*-diphenylphosphinyl, *N*-dimethylthiophosphinyl, *N*-diphenylthiophosphinyl, *N*-dialkyl phosphoryl, *N*-dibenzyl phosphoryl, *N*-diphenyl phosphoryl);
- N-Si Derivatives, N-S Derivatives, and N-Sulfenyl Derivatives: (*N*-benzenesulfenyl, *N*-*o*-nitrobenzenesulfenyl, *N*-2,4-dinitrobenzenesulfenyl, *N*-pentachlorobenzenesulfenyl, *N*-2-nitro-4-methoxybenzenesulfenyl, *N*-triphenylmethylsulfenyl, *N*-3-nitropyridinesulfenyl); and *N*-sulfonyl Derivatives (*N*-*p*-toluenesulfonyl, *N*-benzenesulfonyl, *N*-2,3,6-trimethyl-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethoxybenzenesulfonyl, *N*-2,6-dimethyl-4-methoxybenzenesulfonyl, *N*-pentamethylbenzenesulfonyl, *N*-2,3,5,6,-tetramethyl-4-methoxybenzenesulfonyl, *N*-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethylbenzenesulfonyl, *N*-2,6-dimethoxy-4-methylbenzenesulfonyl, *N*-2,2,5,7,8-pentamethylchroman-6-sulfonyl, *N*-methanesulfonyl, *N*-β-trimethylsilyethanesulfonyl, *N*-9-anthracenesulfonyl, *N*-4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonyl, *N*-benzylsulfonyl, *N*-trifluoromethylsulfonyl, *N*-phenacylsulfonyl).

More typically, protected amino groups include carbamates and amides, still more typically, $-NHC(O)R^1$ or $-N{=}CR^1N(R^1)_2$. Another protecting group, also useful as a prodrug for amino or $-NH(R^5)$, is:



See for example Alexander, J. *et al.* (1996) *J. Med. Chem.* 39:480-486.

Amino acid and polypeptide protecting group and conjugates

An amino acid or polypeptide protecting group of a compound of the invention has the structure $R^{15}NHCH(R^{16})C(O)$-, where R^{15} is H, an amino acid or polypeptide residue, or R^5, and R^{16} is defined below.

R^{16} is lower alkyl or lower alkyl (C_1-C_6) substituted with amino, carboxyl, amide, carboxyl ester, hydroxyl, C_6-C_7 aryl, guanidinyl, imidazolyl, indolyl, sulfhydryl, sulfoxide, and/or alkylphosphate. R^{10} also is taken together with the amino acid α N to form a proline residue (R^{10} = $-CH_2)_3$-). However, R^{10} is generally the side group of a naturally-occurring amino acid such as H, $-CH_3$, $-CH(CH_3)_2$, $-CH_2-CH(CH_3)_2$, $-CHCH_3-CH_2-CH_3$, $-CH_2-C_6H_5$, -$CH_2CH_2-S-CH_3$, $-CH_2OH$, $-CH(OH)-CH_3$, $-CH_2-SH$, $-CH_2-C_6H_4OH$, $-CH_2-CO-NH_2$, $-CH_2$-$CH_2-CO-NH_2$, $-CH_2-COOH$, $-CH_2-CH_2-COOH$, $-(CH_2)_4-NH_2$ and $-(CH_2)_3-NH-C(NH_2)-NH_2$. R_{10} also includes 1-guanidinoprop-3-yl, benzyl, 4-hydroxybenzyl, imidazol-4-yl, indol-3-yl, methoxyphenyl and ethoxyphenyl.

Another set of protecting groups include the residue of an amino-containing compound, in particular an amino acid, a polypeptide, a protecting group, $-NHSO_2R$, $NHC(O)R$, $-N(R)_2$, NH_2 or $-NH(R)(H)$, whereby for example a carboxylic acid is reacted, *i.e.* coupled, with the amine to form an amide, as in $C(O)NR_2$. A phosphonic acid may be reacted with the amine to form a phosphonamidate, as in $-P(O)(OR)(NR_2)$.

In general, amino acids have the structure $R^{17}C(O)CH(R^{16})NH$-, where R^{17} is -OH, -OR, an amino acid or a polypeptide residue. Amino acids are low molecular weight compounds, on the order of less than about 1000 MW and which contain at least one amino or imino group and at least one carboxyl group. Generally the amino acids will be found in nature, *i.e.*, can be detected in biological material such as bacteria or other microbes, plants, animals or man. Suitable amino acids typically are alpha amino acids, *i.e.* compounds characterized by one amino or imino nitrogen atom separated from the carbon atom of one carboxyl group by a single

substituted or unsubstituted alpha carbon atom. Of particular interest are hydrophobic residues such as mono-or di-alkyl or aryl amino acids, cycloalkylamino acids and the like. These residues contribute to cell permeability by increasing the partition coefficient of the parental drug. Typically, the residue does not contain a sulfhydryl or guanidino substituent.

Naturally-occurring amino acid residues are those residues found naturally in plants, animals or microbes, especially proteins thereof. Polypeptides most typically will be substantially composed of such naturally-occurring amino acid residues. These amino acids are glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, methionine, glutamic acid, aspartic acid, lysine, hydroxylysine, arginine, histidine, phenylalanine, tyrosine, tryptophan, proline, asparagine, glutamine and hydroxyproline. Additionally, unnatural amino acids, for example, valanine, phenylglycine and homoarginine are also included. Commonly encountered amino acids that are not gene-encoded may also be used in the present invention. All of the amino acids used in the present invention may be either the D- or L- optical isomer. In addition, other peptidomimetics are also useful in the present invention. For a general review, see Spatola, A. F., in Chemistry and Biochemistry of Amino Acids, Peptides and Proteins, B. Weinstein, eds., Marcel Dekker, New York, p. 267 (1983).

When protecting groups are single amino acid residues or polypeptides they optionally are substituted at R^3 of substituents A^1, A^2 or A^3, or substituted at R_3 of substituents A_1, A_2 or A_3. These conjugates are produced by forming an amide bond between a carboxyl group of the amino acid (or C-terminal amino acid of a polypeptide for example). Similarly, conjugates are formed between R^3 or R_3 and an amino group of an amino acid or polypeptide. Generally, only one of any site in the parental molecule is amidated with an amino acid as described herein, although it is within the scope of this invention to introduce amino acids at more than one permitted site. Usually, a carboxyl group of R^3 is amidated with an amino acid. In general, the α-amino or α-carboxyl group of the amino acid or the terminal amino or carboxyl group of a polypeptide are bonded to the parental functionalities, *i.e.*, carboxyl or amino groups in the amino acid side chains generally are not used to form the amide bonds with the parental compound (although these groups may need to be protected during synthesis of the conjugates as described further below).

With respect to the carboxyl-containing side chains of amino acids or polypeptides it will be understood that the carboxyl group optionally will be blocked, *e.g.*, by R^1, esterified with R^5

or amidated. Similarly, the amino side chains R^{16} optionally will be blocked with R^1 or substituted with R^5.

Such ester or amide bonds with side chain amino or carboxyl groups, like the esters or amides with the parental molecule, optionally are hydrolyzable *in vivo* or *in vitro* under acidic (pH <3) or basic (pH >10) conditions. Alternatively, they are substantially stable in the gastrointestinal tract of humans but are hydrolyzed enzymatically in blood or in intracellular environments. The esters or amino acid or polypeptide amidates also are useful as intermediates for the preparation of the parental molecule containing free amino or carboxyl groups. The free acid or base of the parental compound, for example, is readily formed from the esters or amino acid or polypeptide conjugates of this invention by conventional hydrolysis procedures.

When an amino acid residue contains one or more chiral centers, any of the D, L, meso, threo or erythro (as appropriate) racemates, scalemates or mixtures thereof may be used. In general, if the intermediates are to be hydrolyzed non-enzymatically (as would be the case where the amides are used as chemical intermediates for the free acids or free amines), D isomers are useful. On the other hand,the linkerisomers are more versatile since they can be susceptible to both non-enzymatic and enzymatic hydrolysis, and are more efficiently transported by amino acid or dipeptidyl transport systems in the gastrointestinal tract.

Examples of suitable amino acids whose residues are represented by R^x or R^y include the following:

Glycine;

Aminopolycarboxylic acids, *e.g.*, aspartic acid, β-hydroxyaspartic acid, glutamic acid, β -hydroxyglutamic acid, β-methylaspartic acid, β-methylglutamic acid, β, β-dimethylaspartic acid, γ-hydroxyglutamic acid, β, γ-dihydroxyglutamic acid, β -phenylglutamic acid, γ-methyleneglutamic acid, 3-aminoadipic acid, 2-aminopimelic acid, 2-aminosuberic acid and 2-aminosebacic acid;

Amino acid amides such as glutamine and asparagine;

Polyamino- or polybasic-monocarboxylic acids such as arginine, lysine, β -aminoalanine, γ -aminobutyrine, ornithine, citruline, homoarginine, homocitrulline, hydroxylysine, allohydroxylsine and diaminobutyric acid;

Other basic amino acid residues such as histidine;

Diaminodicarboxylic acids such as α, α'-diaminosuccinic acid, α, α'-diaminoglutaric acid, α, α'-diaminoadipic acid, α, α'-diaminopimelic acid, α, α'-diamino- β-hydroxypimelic acid, α, α'-diaminosuberic acid, α, α'-diaminoazelaic acid, and α, α'-diaminosebacic acid;

Imino acids such as proline, hydroxyproline, allohydroxyproline, γ-methylproline, pipecolic acid, 5-hydroxypipecolic acid, and azetidine-2-carboxylic acid;

A mono- or di-alkyl (typically C_1-C_8 branched or normal) amino acid such as alanine, valine, leucine, allylglycine, butyrine, norvaline, norleucine, heptyline, α-methylserine, α-amino-α-methyl-γ-hydroxyvaleric acid, α-amino- α-methyl-δ-hydroxyvaleric acid, α-amino- α-methyl-ε-hydroxycaproic acid, isovaline, α-methylglutamic acid, α-aminoisobutyric acid, α-aminodiethylacetic acid, α-aminodiisopropylacetic acid, α-aminodi-n-propylacetic acid, α-aminodiisobutylacetic acid, α-aminodi-n-butylacetic acid, α-aminoethylisopropylacetic acid, α-amino-n-propylacetic acid, α-aminodiisoamyacetic acid, α-methylaspartic acid, α-methylglutamic acid, 1-aminocyclopropane-1-carboxylic acid, isoleucine, alloisoleucine, *tert*-leucine, β-methyltryptophan and α-amino- β-ethyl-β-phenylpropionic acid;

β-phenylserinyl;

Aliphatic α-amino-β-hydroxy acids such as serine, β-hydroxyleucine, β-hydroxynorleucine, β -hydroxynorvaline, and α-amino-β-hydroxystearic acid;

α-Amino, α-, γ-, δ- or ε-hydroxy acids such as homoserine, δ -hydroxynorvaline, γ-hydroxynorvaline and ε-hydroxynorleucine residues; canavine and canaline; γ -hydroxyornithine;

2-hexosaminic acids such as D-glucosaminic acid or D-galactosaminic acid;

α-Amino-β-thiols such as penicillamine, β-thiolnorvaline or β-thiolbutyrine;

Other sulfur containing amino acid residues including cysteine; homocystine, β-phenylmethionine, methionine, S-allyl-L-cysteine sulfoxide, 2-thiolhistidine, cystathionine, and thiol ethers of cysteine or homocysteine;

Phenylalanine, tryptophan and ring-substituted α-amino acids such as the phenyl- or cyclohexylamino acids α-aminophenylacetic acid, α-aminocyclohexylacetic acid and α-amino-β-cyclohexylpropionic acid; phenylalanine analogues and derivatives comprising aryl, lower alkyl, hydroxy, guanidino, oxyalkylether, nitro, sulfur or halo-substituted phenyl (*e.g.*, tyrosine, methyltyrosine and o-chloro-, p-chloro-, 3,4-dichloro, *o*-, *m*- or *p*-methyl-, 2,4,6-trimethyl-, 2-ethoxy-5-nitro-, 2-hydroxy-5-nitro- and p-nitro-phenylalanine); furyl-, thienyl-, pyridyl-,

pyrimidinyl-, purinyl- or naphthyl-alanines; and tryptophan analogues and derivatives including kynurenine, 3-hydroxykynurenine, 2-hydroxytryptophan and 4-carboxytryptophan;

α-Amino substituted amino acids including sarcosine (N-methylglycine), N-benzylglycine, N-methylalanine, N-benzylalanine, N-methylphenylalanine, N-benzylphenylalanine, N-methylvaline and N-benzylvaline; and

α-Hydroxy and substituted α -hydroxy amino acids including serine, threonine, allothreonine, phosphoserine and phosphothreonine.

Polypeptides are polymers of amino acids in which a carboxyl group of one amino acid monomer is bonded to an amino or imino group of the next amino acid monomer by an amide bond. Polypeptides include dipeptides, low molecular weight polypeptides (about 1500-5000 MW) and proteins. Proteins optionally contain 3, 5, 10, 50, 75, 100 or more residues, and suitably are substantially sequence-homologous with human, animal, plant or microbial proteins. They include enzymes (*e.g.*, hydrogen peroxidase) as well as immunogens such as KLH, or antibodies or proteins of any type against which one wishes to raise an immune response. The nature and identity of the polypeptide may vary widely.

The polypeptide amidates are useful as immunogens in raising antibodies against either the polypeptide (if it is not immunogenic in the animal to which it is administered) or against the epitopes on the remainder of the compound of this invention.

Antibodies capable of binding to the parental non-peptidyl compound are used to separate the parental compound from mixtures, for example in diagnosis or manufacturing of the parental compound. The conjugates of parental compound and polypeptide generally are more immunogenic than the polypeptides in closely homologous animals, and therefore make the polypeptide more immunogenic for facilitating raising antibodies against it. Accordingly, the polypeptide or protein may not need to be immunogenic in an animal typically used to raise antibodies, *e.g.*, rabbit, mouse, horse, or rat, but the final product conjugate should be immunogenic in at least one of such animals. The polypeptide optionally contains a peptidolytic enzyme cleavage site at the peptide bond between the first and second residues adjacent to the acidic heteroatom. Such cleavage sites are flanked by enzymatic recognition structures, *e.g.*, a particular sequence of residues recognized by a peptidolytic enzyme.

Peptidolytic enzymes for cleaving the polypeptide conjugates of this invention are well known, and in particular include carboxypeptidases. Carboxypeptidases digest polypeptides by

removing C-terminal residues, and are specific in many instances for particular C-terminal sequences. Such enzymes and their substrate requirements in general are well known. For example, a dipeptide (having a given pair of residues and a free carboxyl terminus) is covalently bonded through its α-amino group to the phosphorus or carbon atoms of the compounds herein. In embodiments where W_1 is phosphonate it is expected that this peptide will be cleaved by the appropriate peptidolytic enzyme, leaving the carboxyl of the proximal amino acid residue to autocatalytically cleave the phosphonoamidate bond.

Suitable dipeptidyl groups (designated by their single letter code) are AA, AR, AN, AD, AC, AE, AQ, AG, AH, AI, AL, AK, AM, AF, AP, AS, AT, AW, AY, AV, RA, RR, RN, RD, RC, RE, RQ, RG, RH, RI, RL, RK, RM, RF, RP, RS, RT, RW, RY, RV, NA, NR, NN, ND, NC, NE, NQ, NG, NH, NI, NL, NK, NM, NF, NP, NS, NT, NW, NY, NV, DA, DR, DN, DD, DC, DE, DQ, DG, DH, DI, DL, DK, DM, DF, DP, DS, DT, DW, DY, DV, CA, CR, CN, CD, CC, CE, CQ, CG, CH, CI, CL, CK, CM, CF, CP, CS, CT, CW, CY, CV, EA, ER, EN, ED, EC, EE, EQ, EG, EH, EI, EL, EK, EM, EF, EP, ES, ET, EW, EY, EV, QA, QR, QN, QD, QC, QE, QQ, QG, QH, QI, QL, QK, QM, QF, QP, QS, QT, QW, QY, QV, GA, GR, GN, GD, GC, GE, GQ, GG, GH, GI, GL, GK, GM, GF, GP, GS, GT, GW, GY, GV, HA, HR, HN, HD, HC, HE, HQ, HG, HH, HI, HL, HK, HM, HF, HP, HS, HT, HW, HY, HV, IA, IR, IN, ID, IC, IE, IQ, IG, IH, II, IL, IK, IM, IF, IP, IS, IT, IW, IY, IV, LA, LR, LN, LD, LC, LE, LQ, LG, LH, LI, LL, LK, LM, LF, LP, LS, LT, LW, LY, LV, KA, KR, KN, KD, KC, KE, KQ, KG, KH, KI, KL, KK, KM, KF, KP, KS, KT, KW, KY, KV, MA, MR, MN, MD, MC, ME, MQ, MG, MH, MI, ML, MK, MM, MF, MP, MS, MT, MW, MY, MV, FA, FR, FN, FD, FC, FE, FQ, FG, FH, FI, FL, FK, FM, FF, FP, FS, FT, FW, FY, FV, PA, PR, PN, PD, PC, PE, PQ, PG, PH, PI, PL, PK, PM, PF, PP, PS, PT, PW, PY, PV, SA, SR, SN, SD, SC, SE, SQ, SG, SH, SI, SL, SK, SM, SF, SP, SS, ST, SW, SY, SV, TA, TR, TN, TD, TC, TE, TQ, TG, TH, TI, TL, TK, TM, TF, TP, TS, TT, TW, TY, TV, WA, WR, WN, WD, WC, WE, WQ, WG, WH, WI, WL, WK, WM, WF, WP, WS, WT, WW, WY, WV, YA, YR, YN, YD, YC, YE, YQ, YG, YH, YI, YL, YK, YM, YF, YP, YS, YT, YW, YY, YV, VA, VR, VN, VD, VC, VE, VQ, VG, VH, VI, VL, VK, VM, VF, VP, VS, VT, VW, VY and VV.

Tripeptide residues are also useful as protecting groups. When a phosphonate is to be protected, the sequence $-X^4$-pro-X^5- (where X^4 is any amino acid residue and X^5 is an amino acid residue, a carboxyl ester of proline, or hydrogen) will be cleaved by luminal carboxypeptidase to

yield X^4 with a free carboxyl, which in turn is expected to autocatalytically cleave the phosphonoamidate bond. The carboxy group of X^5 optionally is esterified with benzyl.

Dipeptide or tripeptide species can be selected on the basis of known transport properties and/or susceptibility to peptidases that can affect transport to intestinal mucosal or other cell types. Dipeptides and tripeptides lacking an α-amino group are transport substrates for the peptide transporter found in brush border membrane of intestinal mucosal cells (Bai, J.P.F., (1992) *Pharm Res.* 9:969-978). Transport competent peptides can thus be used to enhance bioavailability of the amidate compounds. Di- or tripeptides having one or more amino acids in the D configuration are also compatible with peptide transport and can be utilized in the amidate compounds of this invention. Amino acids in the D configuration can be used to reduce the susceptibility of a di- or tripeptide to hydrolysis by proteases common to the brush border such as aminopeptidase N. In addition, di- or tripeptides alternatively are selected on the basis of their relative resistance to hydrolysis by proteases found in the lumen of the intestine. For example, tripeptides or polypeptides lacking asp and/or glu are poor substrates for aminopeptidase A, di- or tripeptides lacking amino acid residues on the N-terminal side of hydrophobic amino acids (leu, tyr, phe, val, trp) are poor substrates for endopeptidase, and peptides lacking a pro residue at the penultimate position at a free carboxyl terminus are poor substrates for carboxypeptidase P. Similar considerations can also be applied to the selection of peptides that are either relatively resistant or relatively susceptible to hydrolysis by cytosolic, renal, hepatic, serum or other peptidases. Such poorly cleaved polypeptide amidates are immunogens or are useful for bonding to proteins in order to prepare immunogens.

Prototype compounds contain at least one functional group capable of bonding to the phosphorus atom in the phosphonate moiety. The phosphonate candidate compounds are cleaved intracellularly after they have reached the desired site of action, *e.g.*, inside a lymphoid cell. The mechanism by which this occurs is further described below in the examples. As noted, the free acid of the phosphonate is phosphorylated in the cell..

From the foregoing, it will be apparent that many different prototypes can be derivatized in accord with the present invention. Numerous such prototypes are specifically mentioned herein. However, it should be understood that the discussion of anti-HIVdrug families and their specific members for derivatization according to this invention is not intended to be exhaustive, but merely illustrative.

When the prototype compound contains multiple reactive hydroxyl functions, a mixture of intermediates and final products may be obtained. In the unusual case in which all hydroxy groups are approximately equally reactive, there is not expected to be a single, predominant product, as each mono-substituted product will be obtained in approximately equal amounts, while a lesser amount of multiple-substituted candidate compound will also result. Generally speaking, however, one of the hydroxyl groups will be more susceptible to substitution than the other(s), *e.g.*, a primary hydroxyl will be more reactive than a secondary hydroxyl, an unhindered hydroxyl will be more reactive than a hindered one. Consequently, the major product will be a mono-substituted one in which the most reactive hydroxyl has been derivatized while other mono-substituted and multiply-substituted products may be obtained as minor products.

Stereoisomers

The candidate compounds may have chiral centers, *e.g.*, chiral carbon or phosphorus atoms. The compounds thus include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers. In addition, the compounds include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. In other words, the chiral centers apparent from the depictions are provided as the chiral isomers or racemic mixtures. Both racemic and diastereomeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all suitable for use as candidate compounds. The racemic mixtures are separated into their individual, substantially optically pure isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, *e.g.*, acids or bases followed by conversion back to the optically active substances. In most instances, the desired optical isomer is synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.

The compounds can also exist as tautomeric isomers in certain cases. All though only one delocalized resonance structure may be depicted, all such forms are contemplated within the scope of the invention. For example, ene-amine tautomers can exist for purine, pyrimidine, imidazole, guanidine, amidine, and tetrazole systems and all their possible tautomeric forms are within the scope of the invention.

The optimal absolute configuration at the phosphorus atom for use in candidate compounds is that of GS-7340, depicted in the examples.

Salts and Hydrates

Any reference to any of the compounds of the invention also includes a reference to a physiologically acceptable salt thereof. Examples of physiologically acceptable salts of the compounds of the invention include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth (for example, magnesium), ammonium and NX_4^+ (wherein X is C_1-C_4 alkyl). Physiologically acceptable salts of a hydrogen atom or an amino group include salts of organic carboxylic acids such as acetic, benzoic, lactic, fumaric, tartaric, maleic, malonic, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids; and inorganic acids, such as hydrochloric, sulfuric, phosphoric and sulfamic acids.

Physiologically acceptable salts of a compound of an hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and NX_4^+ (wherein X is independently selected from H or a C_1-C_4 alkyl group).

For therapeutic use, salts of active ingredients of the candidate compounds will be physiologically acceptable, *i.e.* they will be salts derived from a physiologically acceptable acid or base. However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable compound. All salts, whether or not derived form a physiologically acceptable acid or base, are within the scope of the present invention.

Pharmaceutically acceptable non-toxic salts of candidate compounds containing, for example, Na^+, Li^+, K^+, Ca^{+2} and Mg^{+2}, fall within the scope herein. Such salts may include those derived by combination of appropriate cations such as alkali and alkaline earth metal ions or ammonium and quaternary amino ions with an acid anion moiety, typically a carboxylic acid. Monovalent salts are preferred if a water soluble salt is desired.

Metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention. Examples of metal salts which are prepared in this way are salts containing Li^+, Na^+, and K^+. A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal compound.

In addition, salts may be formed from acid addition of certain organic and inorganic acids, *e.g.*, HCl, HBr, H_2SO_4, H_3PO_4 or organic sulfonic acids, to basic centers, typically amines, or to acidic groups. Finally, it is to be understood that the compositions herein comprise compounds of the invention in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

Salts of the candidate compounds with amino acids also fall within the scope of this invention. Any of the amino acids described above are suitable, especially the naturally-occurring amino acids found as protein components, although the amino acid typically is one bearing a side chain with a basic or acidic group, *e.g.*, lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

Methods for Assay of Anti-HIV Activity

The anti-HIV activity of a candidate compound is assayed by any method heretofore known for determining inhibition of growth, replication, or other characteristic of HIV infection, including direct and indirect methods of detecting HIV activity. Quantitative, qualitative, and semiquantitative methods of determining HIV activity are all contemplated. Typically any one of the *in vitro* or cell culture screening methods known to the art are employed, as are clinical trials in humans, studies in animal models (SIV), and the like. In screening candidate compounds it should be kept in mind that the results of enzyme assays may not correlate with cell culture assays. Thus, a cell based assay is often the primary screening tool. Candidate compounds having an *in vitro* Ki (inhibitory constant) of less then about 5×10^{-6} M, typically less than about 1×10^{-7} M and preferably less than about 5×10^{-8} M are preferred for *in vivo* development, but the analytical point of selection of a candidate compound for further development is essentially a matter of choice.

Methods of Inhibition of HIV Protease

Another aspect of the invention relates to methods of inhibiting the activity of HIV protease comprising the step of treating a sample suspected of containing HIV with a composition of the invention.

Compositions of the invention may act as inhibitors of HIV protease, as intermediates for such inhibitors or have other utilities as described below. The inhibitors will bind to locations on the surface or in a cavity of HIV protease having a geometry unique to HIV protease.

Compositions binding HIV protease may bind with varying degrees of reversibility. Those compounds binding substantially irreversibly are ideal candidates for use in this method of the invention. Once labeled, the substantially irreversibly binding compositions are useful as probes for the detection of HIV protease. Accordingly, the invention relates to methods of detecting HIV protease in a sample suspected of containing HIV protease comprising the steps of: treating a sample suspected of containing HIV protease with a composition comprising a compound of the invention bound to a label; and observing the effect of the sample on the activity of the label. Suitable labels are well known in the diagnostics field and include stable free radicals, fluorophores, radioisotopes, enzymes, chemiluminescent groups and chromogens. The compounds herein are labeled in conventional fashion using functional groups such as hydroxyl, carboxyl, sulfhydryl or amino.

Within the context of the invention, samples suspected of containing HIV protease include natural or man-made materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct samples such as extracts of cells, particularly recombinant cells synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing an organism which produces HIV protease, frequently a pathogenic organism such as HIV. Samples can be contained in any medium including water and organic solvent\water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

The treating step of the invention comprises adding the composition of the invention to the sample or it comprises adding a precursor of the composition to the sample. The addition step comprises any method of administration as described above.

If desired, the activity of HIV protease after application of the composition can be observed by any method including direct and indirect methods of detecting HIV protease activity. Quantitative, qualitative, and semiquantitative methods of determining HIV protease activity are all contemplated. Typically one of the screening methods described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

Organisms that contain HIV protease include the HIV virus. The compounds of this invention are useful in the treatment or prophylaxis of HIV infections in animals or in man.

However, in screening compounds capable of inhibiting human immunodeficiency viruses, it should be kept in mind that the results of enzyme assays may not correlate with cell culture assays. Thus, a cell based assay should be the primary screening tool.

Screens for HIV protease Inhibitors

Compositions of the invention are screened for inhibitory activity against HIV protease by any of the conventional techniques for evaluating enzyme activity. Within the context of the invention, typically compositions are first screened for inhibition of HIV protease *in vitro* and compositions showing inhibitory activity are then screened for activity *in vivo*. Compositions having *in vitro* Ki (inhibitory constants) of less then about 5×10^{-6} M, typically less than about 1×10^{-7} M and preferably less than about 5×10^{-8} M are preferred for *in vivo* use.

Useful *in vitro* screens have been described in detail and will not be elaborated here. However, the examples describe suitable *in vitro* assays.

Methods of Inhibition of HIV RT

Another aspect of the invention relates to methods of inhibiting the activity of HIV RT comprising the step of treating a sample suspected of containing HIV RT with a compound of the invention.

Compositions of the invention may act as inhibitors of HIV RT, as intermediates for such inhibitors or have other utilities as described below. The inhibitors will bind to locations on the surface or in a cavity of HIV RT having a geometry unique to HIV RT. Compositions binding HIV RT may bind with varying degrees of reversibility. Those compounds binding substantially irreversibly are ideal candidates for use in this method of the invention. Once labeled, the substantially irreversibly binding compositions are useful as probes for the detection of HIV RT. Accordingly, the invention relates to methods of detecting HIV RT in a sample suspected of containing HIV RT comprising the steps of: treating a sample suspected of containing HIV RT with a composition comprising a compound of the invention bound to a label; and observing the effect of the sample on the activity of the label. Suitable labels are well known in the diagnostics field and include stable free radicals, fluorophores, radioisotopes, enzymes, chemiluminescent groups and chromogens. The compounds herein are labeled in conventional fashion using functional groups such as hydroxyl, amino, carboxyl, or sulfhydryl.

Within the context of the invention samples suspected of containing HIV RT include natural or man-made materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct samples such as extracts of cells, particularly recombinant cells synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing an organism which produces HIV RT, frequently a pathogenic organism such as an HIV virus. Samples can be contained in any medium including water and organic solvent\water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

The treating step of the invention comprises adding the composition of the invention to the sample or it comprises adding a precursor of the composition to the sample. The addition step comprises any method of administration as described above.

If desired, the activity of HIV RT after application of the composition can be observed by any method including direct and indirect methods of detecting HIV RT activity. Quantitative, qualitative, and semiquantitative methods of determining HIV RT activity are all contemplated. Typically one of the screening methods described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

Organisms that contain HIV RT include the HIV virus. The compounds of this invention are useful in the treatment or prophylaxis of HIV infections in animals or in man.

However, in screening compounds capable of inhibiting HIV RT viruses it should be kept in mind that the results of enzyme assays may not correlate with cell culture assays. Thus, a cell based assay should be the primary screening tool.

Screens for HIV RT Inhibitors

Compositions of the invention are screened for inhibitory activity against HIV RT by any of the conventional techniques for evaluating enzyme activity. Within the context of the invention, typically compositions are first screened for inhibition of HIV RT *in vitro* and compositions showing inhibitory activity are then screened for activity *in vivo*. Certain compounds of the invention have *in vitro* Ki (inhibitory constants) of less then about 5×10^{-6} M, and typically less than about 1×10^{-7} M.

Pharmaceutical Formulations

Candidate compounds selected for further development *in vivo* are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of candidate compounds suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the

active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

For infections of the eye or other external tissues *e.g.*, mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, *i.e.* an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include TWEEN® 60, SPAN® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

Pharmaceutical formulations according to the present invention comprise a combination according to the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (*e.g.*, lecithin), a condensation product of an alkylene oxide with a fatty acid (*e.g.*, polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (*e.g.*, heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (*e.g.*, polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the candidate compounds may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring

phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the candidate compounds may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns (including particle sizes in a range between 0.1 and 500 microns in increments microns such as 0.5, 1, 30 microns, 35 microns, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of HIV infections as described below.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of candidate compounds may include other agents conventional in the art

having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

Compounds of the invention are used to provide controlled release pharmaceutical formulations containing as active ingredient one or more compounds of the invention ("controlled release formulations") in which the release of the active ingredient are controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given active ingredient.

An effective dose of candidate compound depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses) or against an active HIV infection, the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. It can be expected to be from about 0.0001 to about 100 mg/kg body weight per day. Typically, from about 0.01 to about 10 mg/kg body weight per day. More typically, from about .01 to about 5 mg/kg body weight per day. More typically, from about .05 to about 0.5 mg/kg body weight per day. For example, the daily candidate dose for an adult human of approximately 70 kg body weight will range from 1 mg to 1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses.

Routes of Administration

One or more candidate compounds (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally.

Combination Therapy

Candidate compounds are also used in combination with other active ingredients. Such combinations are selected based on the condition to be treated, cross-reactivities of ingredients and pharmaco- compounds. Other active ingredients include adefovir dipivoxil and/or any other product currently marketed for therapy of HIV infection.properties. It is also possible to combine any compound of the invention with one or more other active ingredients in a unitary dosage form for simultaneous or sequential administration to an HIV infected patient. The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations. Second and third active ingredients in the combination may have anti-HIV activity and include HIV.

The combination therapy may be synergistic, *i.e.* the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, *e.g.*, in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, *i.e.* serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together. A synergistic anti-viral effect denotes an antiviral effect which is greater than the predicted purely additive effects of the individual compounds of the combination.

Metabolites of the Candidate Compounds

The candidate compounds are metabolized *in vivo*. In particular, the group R^x is hydrolytically cleaved to produce a charged metabolite, and in some cases the substituents on the phosphonate such as $-Y^2[P((=Y^1)(Y^2))_{m2}R^x]_2$ are hydrolyzed as well. An example showing exemplary metabolites is found in the examples herein. While this example is concerned with the metabolites of GS-7340, a nucleotide analogue, the metabolic changes to be found with candidate compounds are believed to be substantially the same at the phosphonate substituent. This charged metabolite functions as an intracellular depot form of the candidate. However,

other changes may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, candidate compounds include metabolites of candidate compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (*e.g.*, C^{14} or H^3) compound of the invention, administering it parenterally in a detectable dose (*e.g.*, greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, *e.g.*, by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the candidate compounds even if they possess no HIV inhibitory activity of their own.

Recipes and methods for determining stability of compounds in surrogate gastrointestinal secretions are known. Compounds are defined herein as stable in the gastrointestinal tract where less than about 50 mole percent of the protected groups are deprotected in surrogate intestinal or gastric juice upon incubation for 1 hour at 37 °C. Simply because the compounds are stable to the gastrointestinal tract does not mean that they cannot be hydrolyzed *in vivo*. The phosphonate prodrugs of the invention typically will be stable in the digestive system but are substantially hydrolyzed to the parental drug in the digestive lumen, liver or other metabolic organ, or within cells in general.

Exemplary Methods of Making Candidate Compounds

The candidate compounds are prepared by any of the applicable techniques of organic synthesis. Many such techniques are well known in the art. However, many of the known techniques are elaborated in Compendium of Organic Synthetic Methods (John Wiley & Sons, New York), Vol. 1, Ian T. Harrison and Shuyen Harrison, 1971; Vol. 2, Ian T. Harrison and Shuyen Harrison, 1974; Vol. 3, Louis S. Hegedus and Leroy Wade, 1977; Vol. 4, Leroy G.

Wade, Jr., 1980; Vol. 5, Leroy G. Wade, Jr., 1984; and Vol. 6, Michael B. Smith; as well as March, J., Advanced Organic Chemistry, Third Edition, (John Wiley & Sons, New York, 1985), Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern Organic Chemistry. In 9 Volumes, Barry M. Trost, Editor-in-Chief (Pergamon Press, New York, 1993 printing).

Dialkyl phosphonates may be prepared according to the methods of: Quast *et al.* (1974) *Synthesis* 490; Stowell *et al.* (1990) *Tetrahedron Lett.* 3261; US Patent No. 5663159.

In general, synthesis of phosphonate esters is achieved by coupling a nucleophile amine or alcohol with the corresponding activated phosphonate electrophilic precursor. For example, chlorophosphonate addition on to 5'-hydroxy of nucleoside is a well known method for preparation of nucleoside phosphate monoesters. The activated precursor can be prepared by several well known methods. Chlorophosphonates useful for synthesis of the prodrugs are prepared from the substituted-1,3-propanediol (Wissner, *et al.*, (1992) *J. Med Chem.* 35:1650). Chlorophosphonates are made by oxidation of the corresponding chlorophospholanes (Anderson, *et al.*, (1984) *J. Org. Chem.* 49:1304) which are obtained by reaction of the substituted diol with phosphorus trichloride. Alternatively, the chlorophosphonate agent is made by treating substituted-1,3-diols with phosphorusoxychloride (Patois, *et al.*, (1990) *J. Chem. Soc. Perkin Trans. I,* 1577). Chlorophosphonate species may also be generated in situ from corresponding cyclic phosphites (Silverburg, *et al.*, (1996) *Tetrahedron Lett.*, 37:771-774), which in turn can be either made from chlorophospholane or phosphoramidate intermediate. The phosphoroflouridate intermediate prepared either from pyrophosphate or phosphoric acid may also act as precursor in preparation of cyclic prodrugs (Watanabe *et al.*, (1988) *Tetrahedron Lett.*, 29:5763-66).

Candidate compounds comprising a prodrug functionality may also be prepared from the free acid by Mitsunobu reactions (Mitsunobu, (1981) *Synthesis*, 1; Campbell, (1992) *J. Org. Chem.*, 52:6331), and other acid coupling reagents including, but not limited to, carbodiimides (Alexander, *et al.*, (1994) *Collect. Czech. Chem. Commun.* 59:1853; Casara, *et al.*, (1992) *Bioorg. Med. Chem. Lett.*, 2:145; Ohashi, *et al.*, (1988) *Tetrahedron Lett.*, 29:1189), and benzotriazolyloxytris-(dimethylamino)phosphonium salts (Campagne, *et al.*, (1993) *Tetrahedron Lett.*, 34:6743).

Aryl halides undergo Ni^{+2} catalyzed reaction with phosphite derivatives to give aryl phosphonate containing compounds (Balthazar, *et al.* (1980) *J. Org. Chem.* 45:5425).

Phosphonates may also be prepared from the chlorophosphonate in the presence of a palladium catalyst using aromatic triflates (Petrakis, *et al.*, (1987) *J. Am. Chem. Soc.* 109:2831; Lu, *et al.*, (1987) *Synthesis*, 726). In another method, aryl phosphonate esters are prepared from aryl phosphates under anionic rearrangement conditions (Melvin (1981) *Tetrahedron Lett.* 22:3375; Casteel, *et al.*, (1991) *Synthesis*, 691). N-Alkoxy aryl salts with alkali metal derivatives of cyclic alkyl phosphonate provide general synthesis for heteroaryl-2-phosphonate linkers (Redmore (1970) *J. Org. Chem.* 35:4114). These above mentioned methods can also be extended to compounds where the W^5 group is a heterocycle. Cyclic-1,3-propanyl prodrugs of phosphonates are also synthesized from phosphonic diacids and substituted propane-1,3-diols using a coupling reagent such as 1,3-dicyclohexylcarbodiimide (DCC) in presence of a base (*e.g.*, pyridine). Other carbodiimide based coupling agents like 1,3-disopropylcarbodiimide or water soluble reagent, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) can also be utilized for the synthesis of cyclic phosphonate prodrugs.

The carbamoyl group may be formed by reaction of a hydroxy group according to the methods known in the art, including the teachings of Ellis, U.S. 2002/0103378 A1 and Hajima, U.S. 6,018,049.

A number of exemplary methods for the preparation of the candidate compounds are provided below. These methods are intended to illustrate the nature of such preparations and do not limit the scope of this invention. Many of the compounds set forth below have been screened and demonstrated to have anti-HIV activity. In view of this these compounds are no longer candidate compounds for use in the screening method of this invention. However, they are illustrative of the manner in which the artisan can substitute prototype compouns with A^3 in various ways. In addition, taken cumulatively, they are illustrative of the typical component candidate compounds to be found in a screening library.

Generally, the reaction conditions such as temperature, reaction time, solvents, work-up procedures, and the like, will be those common in the art for the particular reaction to be performed. The cited reference material, together with material cited therein, contains detailed descriptions of such conditions. Typically the temperatures will be -100°C to 200°C, solvents will be aprotic or protic, and reaction times will be 10 seconds to 10 days. Work-up typically consists of quenching any unreacted reagents followed by partition between a water/organic layer system (extraction) and separating the layer containing the product.

Oxidation and reduction reactions are typically carried out at temperatures near room temperature (about 20 °C), although for metal hydride reductions frequently the temperature is reduced to 0 °C to -100 °C, solvents are typically aprotic for reductions and may be either protic or aprotic for oxidations. Reaction times are adjusted to achieve desired conversions.

Condensation reactions are typically carried out at temperatures near room temperature, although for non-equilibrating, kinetically controlled condensations reduced temperatures (0 °C to -100 °C) are also common. Solvents can be either protic (common in equilibrating reactions) or aprotic (common in kinetically controlled reactions).

Standard synthetic techniques such as azeotropic removal of reaction by-products and use of anhydrous reaction conditions (*e.g.*, inert gas environments) are common in the art and will be applied when applicable.

Schemes

General aspects of these exemplary methods are described below and in the Examples. Each of the products of the following processeses are optionally separated, isolated, and/or purified prior to its use in subsequent processes.

The terms "treated", "treating", "treatment", and the like, mean contacting, mixing, reacting, allowing to react, bringing into contact, and other terms common in the art for indicating that one or more chemical entities is treated in such a manner as to convert it to one or more other chemical entities. This means that "treating compound one with compound two" is synonymous with "allowing compound one to react with compound two", "contacting compound one with compound two", "reacting compound one with compound two", and other expressions common in the art of organic synthesis for reasonably indicating that compound one was "treated", "reacted", "allowed to react", etc., with compound two.

"Treating" indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal concentrations (0.01M to 10M, typically 0.1M to 1M), temperatures (-100 °C to 250 °C, typically -78 °C to 150 °C, more typically -78 °C to 100 °C, still more typically 0 °C to 100 °C), reaction vessels (typically glass, plastic, metal), solvents, pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or argon for oxygen or water sensitive), etc., are intended unless otherwise indicated. The knowledge of similar reactions known in the art of organic synthesis are used in selecting the conditions and apparatus for "treating" in a given process. In particular, one of ordinary skill in the art of

organic synthesis selects conditions and apparatus reasonably expected to successfully carry out the chemical reactions of the described processes based on the knowledge in the art.

Modifications of each of the exemplary schemes above and in the examples (hereafter "exemplary schemes") leads to various analogs of the candidate compounds. The above cited citations describing suitable methods of organic synthesis are applicable to such modifications.

In each of the exemplary schemes it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium, and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed (SMB) and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

Selection of appropriate methods of separation depends on the nature of the materials involved. These include boiling point and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply techniques most likely to achieve the desired separation.

A single stereoisomer, *e.g.*, an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents (Stereochemistry of Carbon Compounds, (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) *J. Chromatogr.*, 113:(3) 283-302). Racemic

mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions.

Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, α-methyl-β-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts.

Alternatively, by method (2), the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched xanthene. A method of determining optical purity involves making chiral esters, such as a menthyl ester, *e.g.*, (-) menthyl chloroformate in the presence of base, or Mosher ester, α-methoxy-α-(trifluoromethyl)phenyl acetate (Jacob III. (1982) *J. Org. Chem.* 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111). By method (3), a racemic mixture of two enantiomers can be separated by chromatography using a chiral stationary phase (Chiral Liquid Chromatography (1989) W. J. Lough, Ed. Chapman and Hall, New York; Okamoto, (1990) *J. of Chromatogr.* 513:375-378). Enriched or purified enantiomers can be distinguished by methods used to distinguish other chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

The articles "and" and "or" shall be construed as meaning "and/or" unless otherwise required by context or useage. Use of "and/or" herein shall not be construed as foreclosing "and/or" when only "and" or "or" are employed in other circumstances.

This invention includes all novel and unobvious compounds disclosed herein, whether or not such compounds are described in the context of methods or other disclosure and whether or not such compounds are claimed upon filing or are set forth in the summary of invention.

The invention has been described in detail sufficient to allow one of ordinary skill in the art to make and use the subject matter of the following examples. It is apparent that certain modifications of the methods and compositions of the following examples can be made within the scope and spirit of the invention.

Examples General Section

Some Examples have been performed multiple times. In repeated Examples, reaction conditions such as time, temperature, concentration and the like, and yields were within normal experimental ranges. In repeated Examples where significant modifications were made, these have been noted where the results varied significantly from those described. In Examples where different starting materials were used, these are noted. When the repeated Examples refer to a "corresponding" analog of a compound, such as a "corresponding ethyl ester", this intends that an otherwise present group, in this case typically a methyl ester, is taken to be the same group modified as indicated.

Exemplary Methods of Making the Compounds of the Invention.

The invention provides many methods of making the compositions of the invention. The compositions are prepared by any of the applicable techniques of organic synthesis. Many such techniques are well known in the art. Such as those elaborated in Compendium of Organic Synthetic Methods (John Wiley & Sons, New York), Vol. 1, Ian T. Harrison and Shuyen Harrison, 1971; Vol. 2, Ian T. Harrison and Shuyen Harrison, 1974; Vol. 3, Louis S. Hegedus and Leroy Wade, 1977; Vol. 4, Leroy G. Wade, Jr., 1980; Vol. 5, Leroy G. Wade, Jr., 1984; and Vol. 6, Michael B. Smith; as well as March, J., Advanced Organic Chemistry, Third Edition, (John Wiley & Sons, New York, 1985), Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern Organic Chemistry. In 9 Volumes, Barry M. Trost, Editor-in-Chief (Pergamon Press, New York, 1993 printing).

Dialkyl phosphonates may be prepared according to the methods of: Quast *et al.* (1974) *Synthesis* 490; Stowell *et al.* (1990) *Tetrahedron Lett.* 3261; US Patent No. 5663159.

In general, synthesis of phosphonate esters is achieved by coupling a nucleophile amine or alcohol with the corresponding activated phosphonate electrophilic precursor for example, Chlorophosphonate addition on to 5'-hydroxy of nucleoside is a well known method for preparation of nucleoside phosphate monoesters. The activated precursor can be prepared by several well known methods. Chlorophosphonates useful for synthesis of the prodrugs are prepared from the substituted-1,3-propanediol (Wissner, *et al.*, (1992) *J. Med Ch*em. 35:1650). Chlorophosphonates are made by oxidation of the corresponding chlorophospholanes (Anderson, *et al.*, (1984) *J. Org. Chem.* 49:1304) which are obtained by reaction of the substituted diol with phosphorus trichloride. Alternatively, the chlorophosphonate agent is made by treating substituted-1,3-diols with phosphorusoxychloride (Patois, *et al.*, (1990) *J. Chem. Soc. Perkin Trans. I,* 1577). Chlorophosphonate species may also be generated in situ from corresponding cyclic phosphites (Silverburg, *et al.*, (1996) *Tetrahedron Lett.*, 37:771-774), which in turn can be either made from chlorophospholane or phosphoramidate intermediate. Phosphoroflouridate intermediate prepared either from pyrophosphate or phosphoric acid may also act as precursor in preparation of cyclic prodrugs (Watanabe *et al.*, (1988) *Tetrahedron lett.*, 29:5763-66). Caution: fluorophosphonate compounds may be highly toxic!

Schemes and Examples

General aspects of these exemplary methods are described below and in the Examples. Each of the products of the following processes is optionally separated, isolated, and/or purified prior to its use in subsequent processes.

A number of exemplary methods for the preparation of the compositions of the invention are provided below. These methods are intended to illustrate the nature of such preparations are not intended to limit the scope of applicable methods.

The terms “treated”, “treating”, “treatment”, and the like, mean contacting, mixing, reacting, allowing to react, bringing into contact, and other terms common in the art for indicating that one or more chemical entities is treated in such a manner as to convert it to one or more other chemical entities. This means that “treating compound one with compound two” is synonymous with “allowing compound one to react with compound two,” “contacting compound one with compound two”, “reacting compound one with compound two”, and other expressions

common in the art of organic synthesis for reasonably indicating that compound one was "treated", "reacted", "allowed to react", etc., with compound two.

"Treating" indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal concentrations (0.01M to 10M, typically 0.1M to 1M), temperatures (-100°C to 250°C, typically -78°C to 150°C, more typically -78°C to 100°C, still more typically 0°C to 100°C), reaction vessels (typically glass, plastic, metal), solvents, pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or argon for oxygen or water sensitive), etc., are intended unless otherwise indicated. The knowledge of similar reactions known in the art of organic synthesis are used in selecting the conditions and apparatus for "treating" in a given process. In particular, one of ordinary skill in the art of organic synthesis selects conditions and apparatus reasonably expected to successfully carry out the chemical reactions of the described processes based on the knowledge in the art.

Modifications of each of the exemplary schemes above and in the examples (hereafter "exemplary schemes") leads to various analogs of the specific exemplary materials produce. The above cited citations describing suitable methods of organic synthesis are applicable to such modifications.

In each of the exemplary schemes it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium, and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed (SMB) and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding

reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point, and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply techniques most likely to achieve the desired separation.

A single stereoisomer, *e.g.*, an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents (Stereochemistry of Carbon Compounds, (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) *J. Chromatogr.*, 113:(3) 283-302). Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions.

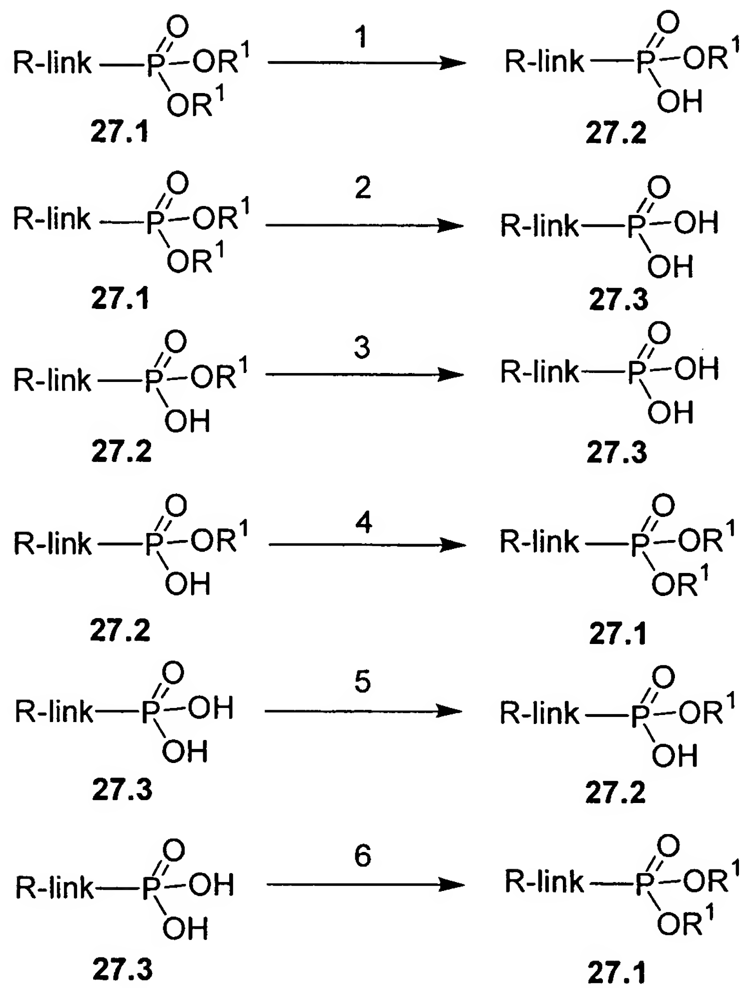
Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, α-methyl-β-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts.

Alternatively, by method (2), the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched xanthene. A method of determining optical purity involves making chiral esters, such as a menthyl ester, *e.g.*, (-) menthyl

chloroformate in the presence of base, or Mosher ester, α-methoxy-α-(trifluoromethyl)phenyl acetate (Jacob III. (1982) *J. Org. Chem.* 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111). By method (3), a racemic mixture of two enantiomers can be separated by chromatography using a chiral stationary phase (Chiral Liquid Chromatography (1989) W. J. Lough, Ed. Chapman and Hall, New York; Okamoto, (1990) *J. of Chromatogr.* 513:375-378). Enriched or purified enantiomers can be distinguished by methods used to distinguish other chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

All literature and patent citations above are hereby expressly incorporated by reference at the locations of their citation. Specifically cited sections or pages of the above cited works are incorporated by reference with specificity. The invention has been described in detail sufficient to allow one of ordinary skill in the art to make and use the subject matter of the following Embodiments. It is apparent that certain modifications of the methods and compositions of the following Embodiments can be made within the scope and spirit of the invention.

Scheme X1



Scheme X1 shows the general interconversions of certain phosphonate compounds: acids $-P(O)(OH)_2$; mono-esters $-P(O)(OR_1)(OH)$; and diesters $-P(O)(OR_1)_2$ in which the R^1 groups are independently selected, and defined herein before, and the phosphorus is attached through a carbon moiety (link, *i.e.* linker), which is attached to the rest of the molecule, *e.g.*, drug or drug intermediate (R). The R^1 groups attached to the phosphonate esters in Scheme X1 may be changed using established chemical transformations. The interconversions may be carried out in the precursor compounds or the final products using the methods described below. The methods employed for a given phosphonate transformation depend on the nature of the substituent R^1. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester **27.1** into the corresponding phosphonate monoester **27.2** (Scheme X1, Reaction 1) can be accomplished by a number of methods. For example, the ester **27.1** in which R^1 is an arylalkyl group such as benzyl, can be converted into the monoester compound **27.2** by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in *J. Org. Chem.*, 1995, 60:2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°C. The conversion of the diester **27.1** in which R^1 is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester **27.2** can be effected by treatment of the ester **27.1** with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters **27.2** in which one of the groups R^1 is arylalkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters **27.2** in which R^1 is alkyl, by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R^1 are alkenyl, such as allyl, can be converted into the monoester **27.2** in which R^1 is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in *J. Org. Chem.*, 38:3224 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester **27.1** or a phosphonate monoester **27.2** into the corresponding phosphonic acid **27.3** (Scheme X1, Reactions 2 and 3) can effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in *J. Chem. Soc., Chem. Comm.*, 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **27.2** in which $R^1$is arylalkyl such as benzyl, can be converted into the corresponding phosphonic acid **27.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxane. A phosphonate monoester **27.2** in which R^1 is alkenyl such as, for example, allyl, can be converted into the phosphonic acid **27.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in *Helv. Chim. Acta.*, 68:618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **27.1** in which R^1 is benzyl is

described in *J. Org. Chem.*, 24:434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **27.1** in which R^1 is phenyl is described in *J. Amer. Chem. Soc.*, 78:2336, 1956.

The conversion of a phosphonate monoester **27.2** into a phosphonate diester **27.1** (Scheme X1, Reaction 4) in which the newly introduced R^1 group is alkyl, arylalkyl, or haloalkyl such as chloroethyl, can be effected by a number of reactions in which the substrate **27.2** is reacted with a hydroxy compound R^1OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **27.1** to the diester **27.1** can be effected by the use of the Mitsunobu reaction. The substrate is reacted with the hydroxy compound R^1OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **27.2** can be transformed into the phosphonate diester **27.1**, in which the introduced R^1 group is alkenyl or arylalkyl, by reaction of the monoester with the halide R^1Br, in which R^1 is as alkenyl or arylalkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **27.2** is transformed into the chloro analog $-P(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $-P(O)(OR^1)Cl$ is then reacted with the hydroxy compound R^1OH, in the presence of a base such as triethylamine, to afford the phosphonate diester **27.1**.

A phosphonic acid $-P(O)(OH)_2$ can be transformed into a phosphonate monoester $-P(O)(OR^1)(OH)$ (Scheme X1, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester $-P(O)(OR^1)_2$ **27.1**, except that only one molar proportion of the component R^1OH or R^1Br is employed.

A phosphonic acid -$P(O)(OH)_2$ **27.3** can be transformed into a phosphonate diester -$P(O)(OR^1)_2$ **27.1** (Scheme X1, Reaction 6) by a coupling reaction with the hydroxy compound R^1OH, in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids **27.3** can be transformed into phosphonic esters **27.1** in which R^1 is aryl, such as phenyl, by means of a coupling reaction employing, for example, phenol and dicyclohexylcarbodiimide in pyridine at about 70°C. Alternatively, phosphonic acids **27.3** can be transformed into phosphonic esters **27.1** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, in the presence of a base such as cesium carbonate, to afford the phosphonic ester **27.1**.

Phosphonate prodrugs of the present invention may also be prepared from the precursor free acid by Mitsunobu reactions (Mitsunobu, (1981) *Synthesis*, 1; Campbell, (1992) *J. Org. Chem.*, 52:6331), and other acid coupling reagents including, but not limited to, carbodiimides (Alexander, *et al.*, (1994) *Collect. Czech. Chem. Commun.* 59:1853; Casara, *et al.*, (1992) *Bioorg. Med. Chem. Lett.*, 2:145; Ohashi, *et al.*, (1988) *Tetrahedron Lett.*, 29:1189), and benzotriazolyloxytris-(dimethylamino)phosphonium salts (Campagne, *et al.*, (1993) *Tetrahedron Lett.*, 34:6743).

Preparation of carboalkoxy-substituted phosphonate bisamidates, monoamidates, diesters and monoesters

A number of methods are available for the conversion of phosphonic acids into amidates and esters. In one group of methods, the phosphonic acid is either converted into an isolated activated intermediate such as a phosphoryl chloride, or the phosphonic acid is activated in situ for reaction with an amine or a hydroxy compound.

The conversion of phosphonic acids into phosphoryl chlorides is accomplished by reaction with thionyl chloride, for example as described in *J. Gen. Chem. USSR*, 1983, 53, 480, *Zh. Obschei Khim.*, 1958, 28, 1063, or *J. Org. Chem.*, 1994, 59, 6144, or by reaction with oxalyl chloride, as described in *J. Am. Chem. Soc.*, 1994, 116, 3251, or *J. Org. Chem.*, 1994, 59, 6144, or by reaction with phosphorus pentachloride, as described in *J. Org. Chem.*, 2001, 66, 329, or in *J. Med. Chem.*, 1995, 38, 1372. The resultant phosphoryl chlorides are then reacted with amines or hydroxy compounds in the presence of a base to afford the amidate or ester products.

Phosphonic acids are converted into activated imidazolyl derivatives by reaction with carbonyl diimidazole, as described in *J. Chem. Soc., Chem. Comm.*, 1991, 312, or *Nucleosides Nucleotides* 2000, 19, 1885. Activated sulfonyloxy derivatives are obtained by the reaction of phosphonic acids with trichloromethylsulfonyl chloride, as described in *J. Med. Chem.* 1995, 38, 4958, or with triisopropylbenzenesulfonyl chloride, as described in *Tetrahedron Lett.*, 1996, 7857, or *Bioorg. Med. Chem. Lett.*, 1998, 8, 663. The activated sulfonyloxy derivatives are then reacted with amines or hydroxy compounds to afford amidates or esters.

Alternatively, the phosphonic acid and the amine or hydroxy reactant are combined in the presence of a diimide coupling agent. The preparation of phosphonic amidates and esters by means of coupling reactions in the presence of dicyclohexyl carbodiimide is described, for example, in *J. Chem. Soc., Chem. Comm.*, 1991, 312, or *J. Med. Chem.*, 1980, 23, 1299 or *Coll. Czech. Chem. Comm.*, 1987, 52, 2792. The use of ethyl dimethylaminopropyl carbodiimide for activation and coupling of phosphonic acids is described in *Tetrahedron Lett.*, 2001, 42, 8841, or *Nucleosides Nucleotides*, 2000, 19, 1885.

A number of additional coupling reagents have been described for the preparation of amidates and esters from phosphonic acids. The agents include Aldrithiol-2, and PYBOP and BOP, as described in *J. Org. Chem.*, 1995, 60, 5214, and *J. Med. Chem.*, 1997, 40, 3842, mesitylene-2-sulfonyl-3-nitro-1,2,4-triazole (MSNT), as described in *J. Med. Chem.*, 1996, 39, 4958, diphenylphosphoryl azide, as described in *J. Org. Chem.*, 1984, 49, 1158, 1-(2,4,6-triisopropylbenzenesulfonyl-3-nitro-1,2,4-triazole (TPSNT) as described in *Bioorg. Med. Chem. Lett.*, 1998, 8, 1013, bromotris(dimethylamino)phosphonium hexafluorophosphate (BroP), as described in *Tetrahedron Lett.*, 1996, 37, 3997, 2-chloro-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphinane, as described in *Nucleosides Nucleotides* 1995, 14, 871, and diphenyl chlorophosphate, as described in *J. Med. Chem.*, 1988, 31, 1305.

Phosphonic acids are converted into amidates and esters by means of the Mitsonobu reaction, in which the phosphonic acid and the amine or hydroxy reactant are combined in the presence of a triaryl phosphine and a dialkyl azodicarboxylate. The procedure is described in *Org. Lett.*, 2001, 3, 643, or *J. Med. Chem.*, 1997, 40, 3842.

Phosphonic esters are also obtained by the reaction between phosphonic acids and halo compounds, in the presence of a suitable base. The method is described, for example, in *Anal.*

Chem., 1987, 59, 1056, or *J. Chem. Soc. Perkin Trans., I,* 1993, 19, 2303, or *J. Med. Chem.*, 1995, 38, 1372, or *Tetrahedron Lett.*, 2002, 43, 1161.

Schemes **1** - **4** illustrate the conversion of phosphonate esters and phosphonic acids into carboalkoxy-substituted phosphorobisamidates (Scheme **1**), phosphoroamidates (Scheme **2**), phosphonate monoesters (Scheme **3**) and phosphonate diesters, (Scheme **4**).

Scheme **1** illustrates various methods for the conversion of phosphonate diesters **1.1** into phosphorobisamidates **1.5**. The diester **1.1**, prepared as described previously, is hydrolyzed, either to the monoester **1.2** or to the phosphonic acid **1.6**. The methods employed for these transformations are described above. The monoester **1.2** is converted into the monoamidate **1.3** by reaction with an aminoester **1.9**, in which the group R^2 is H or alkyl, the group R^4 is an alkylene moiety such as, for example, $CHCH_3$, $CHPr^i$, $CH(CH_2Ph)$, $CH_2CH(CH_3)$ and the like, or a group present in natural or modified aminoacids, and the group R^5 is alkyl. The reactants are combined in the presence of a coupling agent such as a carbodiimide, for example dicyclohexyl carbodiimide, as described in *J. Am. Chem. Soc.*, 1957, 79, 3575, optionally in the presence of an activating agent such as hydroxybenztriazole, to yield the amidate product **1.3**. The amidate-forming reaction is also effected in the presence of coupling agents such as BOP, as described in *J. Org. Chem.*, 1995, 60, 5214, Aldrithiol, PYBOP and similar coupling agents used for the preparation of amides and esters. Alternatively, the reactants **1.2** and **1.9** are transformed into the monoamidate **1.3** by means of a Mitsonobu reaction. The preparation of amidates by means of the Mitsonobu reaction is described in *J. Med. Chem.*, 1995, 38, 2742. Equimolar amounts of the reactants are combined in an inert solvent such as tetrahydrofuran in the presence of a triaryl phosphine and a dialkyl azodicarboxylate. The thus-obtained monoamidate ester **1.3** is then transformed into amidate phosphonic acid **1.4**. The conditions used for the hydrolysis reaction depend on the nature of the R^1 group, as described previously. The phosphonic acid amidate **1.4** is then reacted with an aminoester **1.9**, as described above, to yield the bisamidate product **1.5**, in which the amino substituents are the same or different.

An example of this procedure is shown in Scheme **1**, Example **1**. In this procedure, a dibenzyl phosphonate **1.14** is reacted with diazabicyclooctane (DABCO) in toluene at reflux, as described in *J. Org. Chem.*, 1995, 60, 2946, to afford the monobenzyl phosphonate **1.15**. The product is then reacted with equimolar amounts of ethyl alaninate **1.16** and dicyclohexyl carbodiimide in pyridine, to yield the amidate product **1.17**. The benzyl group is then removed,

for example by hydrogenolysis over a palladium catalyst, to give the monoacid product **1.18**. This compound is then reacted in a Mitsonobu reaction with ethyl leucinate **1.19**, triphenyl phosphine and diethylazodicarboxylate, as described in *J. Med. Chem.*, 1995, 38, 2742, to produce the bisamidate product **1.20**.

Using the above procedures, but employing, in place of ethyl leucinate **1.19** or ethyl alaninate **1.16**, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

Alternatively, the phosphonic acid **1.6** is converted into the bisamidate **1.5** by use of the coupling reactions described above. The reaction is performed in one step, in which case the nitrogen-related substituents present in the product **1.5** are the same, or in two steps, in which case the nitrogen-related substituents can be different.

An example of the method is shown in Scheme **1**, Example **2**. In this procedure, a phosphonic acid **1.6** is reacted in pyridine solution with excess ethyl phenylalaninate **1.21** and dicyclohexylcarbodiimide, for example as described in *J. Chem. Soc.*, *Chem. Comm.*, 1991, 1063, to give the bisamidate product **1.22**.

Using the above procedures, but employing, in place of ethyl phenylalaninate, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

As a further alternative, the phosphonic acid **1.6** is converted into the mono or bis-activated derivative **1.7**, in which Lv is a leaving group such as chloro, imidazolyl, triisopropylbenzenesulfonyloxy, etc. The conversion of phosphonic acids into chlorides **1.7** (Lv = Cl) is effected by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17. The conversion of phosphonic acids into monoimidazolides **1.7** (Lv = imidazolyl) is described in *J. Med. Chem.*, 2002, 45, 1284 and in *J. Chem. Soc. Chem. Comm.*, 1991, 312. Alternatively, the phosphonic acid is activated by reaction with triisopropylbenzenesulfonyl chloride, as described in *Nucleosides and Nucleotides*, 2000, 10, 1885. The activated product is then reacted with the aminoester **1.9**, in the presence of a base, to give the bisamidate **1.5**. The reaction is performed in one step, in which case the nitrogen substituents present in the product **1.5** are the same, or in two steps, via the intermediate **1.11**, in which case the nitrogen substituents can be different.

Examples of these methods are shown in Scheme **1**, Examples **3** and **5**. In the procedure illustrated in Scheme **1**, Example **3**, a phosphonic acid **1.6** is reacted with ten molar equivalents of thionyl chloride, as described in *Zh. Obschei Khim.*, 1958, 28, 1063, to give the dichloro

compound **1.23**. The product is then reacted at reflux temperature in a polar aprotic solvent such as acetonitrile, and in the presence of a base such as triethylamine, with butyl serinate **1.24** to afford the bisamidate product **1.25**.

Using the above procedures, but employing, in place of butyl serinate **1.24**, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

In the procedure illustrated in Scheme **1**, Example **5**, the phosphonic acid **1.6** is reacted, as described in *J. Chem. Soc. Chem. Comm.*, 1991, 312, with carbonyl diimidazole to give the imidazolide **1.32**. The product is then reacted in acetonitrile solution at ambient temperature, with one molar equivalent of ethyl alaninate **1.33** to yield the monodisplacement product **1.34**. The latter compound is then reacted with carbonyl diimidazole to produce the activated intermediate **1.35**, and the product is then reacted, under the same conditions, with ethyl N-methylalaninate **1.33a** to give the bisamidate product **1.36**.

Using the above procedures, but employing, in place of ethyl alaninate **1.33** or ethyl N-methylalaninate **1.33a**, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

The intermediate monoamidate **1.3** is also prepared from the monoester **1.2** by first converting the monoester into the activated derivative **1.8** in which Lv is a leaving group such as halo, imidazolyl etc, using the procedures described above. The product **1.8** is then reacted with an aminoester **1.9** in the presence of a base such as pyridine, to give an intermediate monoamidate product **1.3**. The latter compound is then converted, by removal of the R^1 group and coupling of the product with the aminoester **1.9**, as described above, into the bisamidate **1.5**.

An example of this procedure, in which the phosphonic acid is activated by conversion to the chloro derivative **1.26**, is shown in Scheme **1**, Example **4**. In this procedure, the phosphonic monobenzyl ester **1.15** is reacted, in dichloromethane, with thionyl chloride, as described in *Tetrahedron Lett.*, 1994, 35, 4097, to afford the phosphoryl chloride **1.26**. The product is then reacted in acetonitrile solution at ambient temperature with one molar equivalent of ethyl 3-amino-2-methylpropionate **1.27** to yield the monoamidate product **1.28**. The latter compound is hydrogenated in ethyl acetate over a 5% palladium on carbon catalyst to produce the monoacid product **1.29**. The product is subjected to a Mitsonobu coupling procedure, with equimolar amounts of butyl alaninate **1.30**, triphenyl phosphine, diethylazodicarboxylate and triethylamine in tetrahydrofuran, to give the bisamidate product **1.31**.

Using the above procedures, but employing, in place of ethyl 3-amino-2-methylpropionate **1.27** or butyl alaninate **1.30**, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

The activated phosphonic acid derivative **1.7** is also converted into the bisamidate **1.5** via the diamino compound **1.10**. The conversion of activated phosphonic acid derivatives such as phosphoryl chlorides into the corresponding amino analogs **1.10**, by reaction with ammonia, is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976. The diamino compound **1.10** is then reacted at elevated temperature with a haloester **1.12**, in a polar organic solvent such as dimethylformamide, in the presence of a base such as dimethylaminopyridine or potassium carbonate, to yield the bisamidate **1.5**.

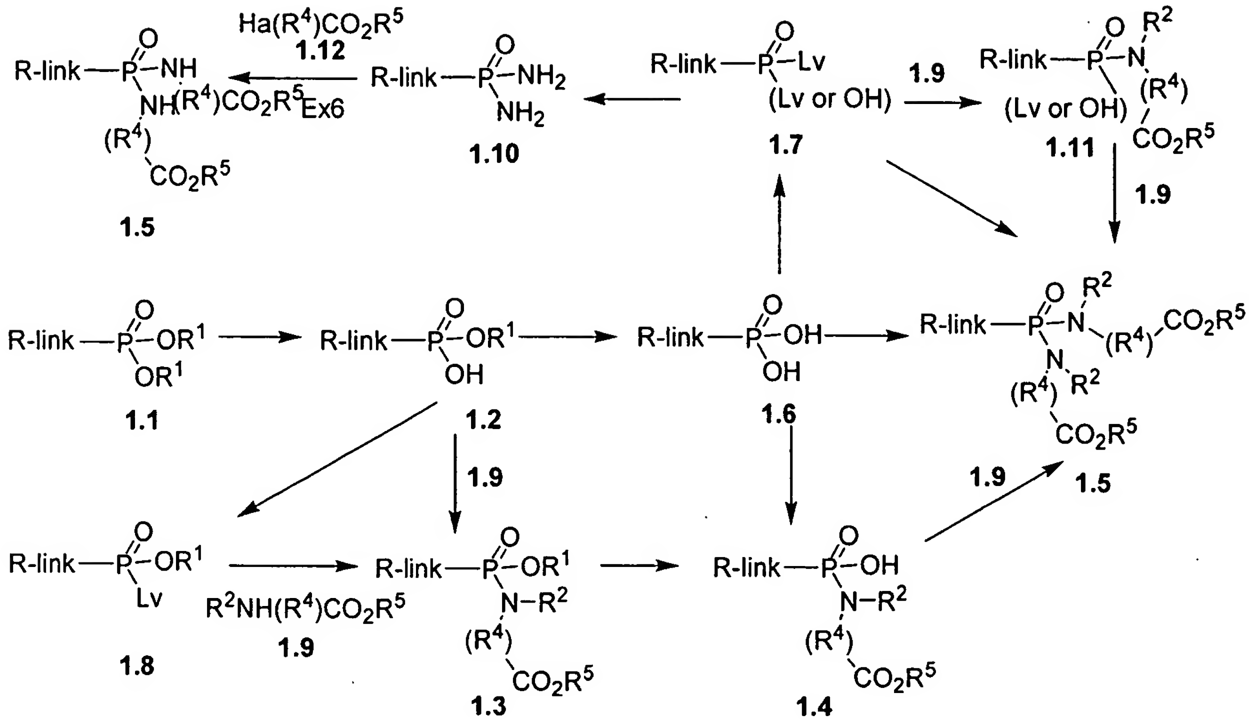
An example of this procedure is shown in Scheme **1**, Example **6**. In this method, a dichlorophosphonate **1.23** is reacted with ammonia to afford the diamide **1.37**. The reaction is performed in aqueous, aqueous alcoholic or alcoholic solution, at reflux temperature. The resulting diamino compound is then reacted with two molar equivalents of ethyl 2-bromo-3-methylbutyrate **1.38**, in a polar organic solvent such as N-methylpyrrolidinone at ca. 150°C, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, to afford the bisamidate product **1.39**.

Using the above procedures, but employing, in place of ethyl 2-bromo-3-methylbutyrate **1.38**, different haloesters **1.12** the corresponding products **1.5** are obtained.

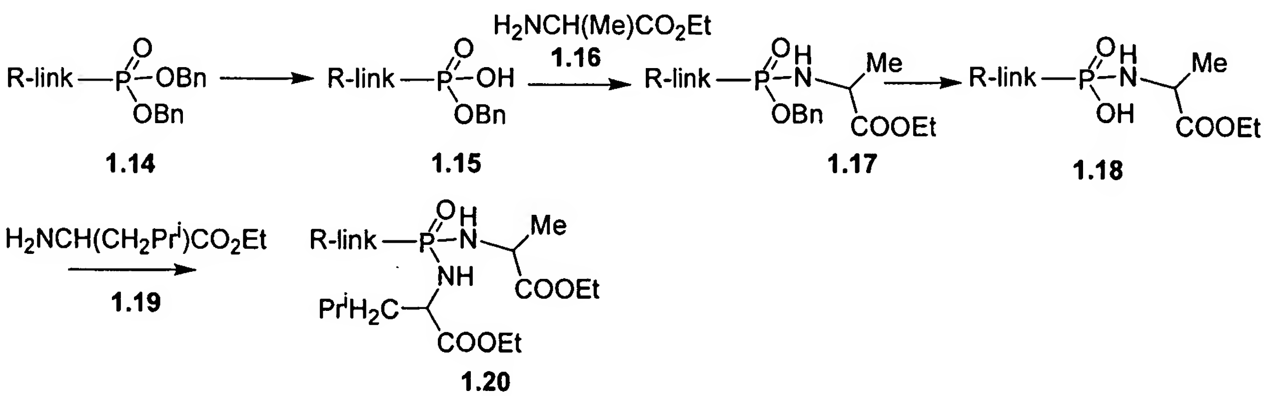
The procedures shown in Scheme **1** are also applicable to the preparation of bisamidates in which the aminoester moiety incorporates different functional groups. Scheme **1**, Example **7** illustrates the preparation of bisamidates derived from tyrosine. In this procedure, the monoimidazolide **1.32** is reacted with propyl tyrosinate **1.40**, as described in Example **5**, to yield the monoamidate **1.41**. The product is reacted with carbonyl diimidazole to give the imidazolide **1.42**, and this material is reacted with a further molar equivalent of propyl tyrosinate to produce the bisamidate product **1.43**.

Using the above procedures, but employing, in place of propyl tyrosinate **1.40**, different aminoesters **1.9**, the corresponding products **1.5** are obtained. The aminoesters employed in the two stages of the above procedure can be the same or different, so that bisamidates with the same or different amino substituents are prepared.

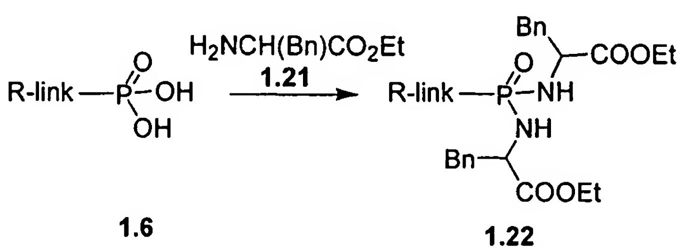
Scheme 1



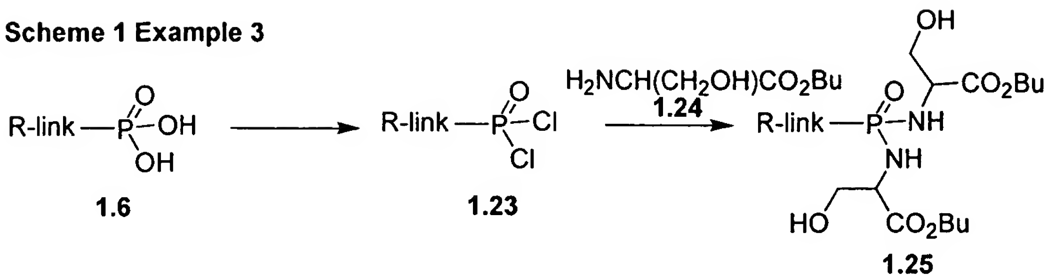
Scheme 1 Example 1



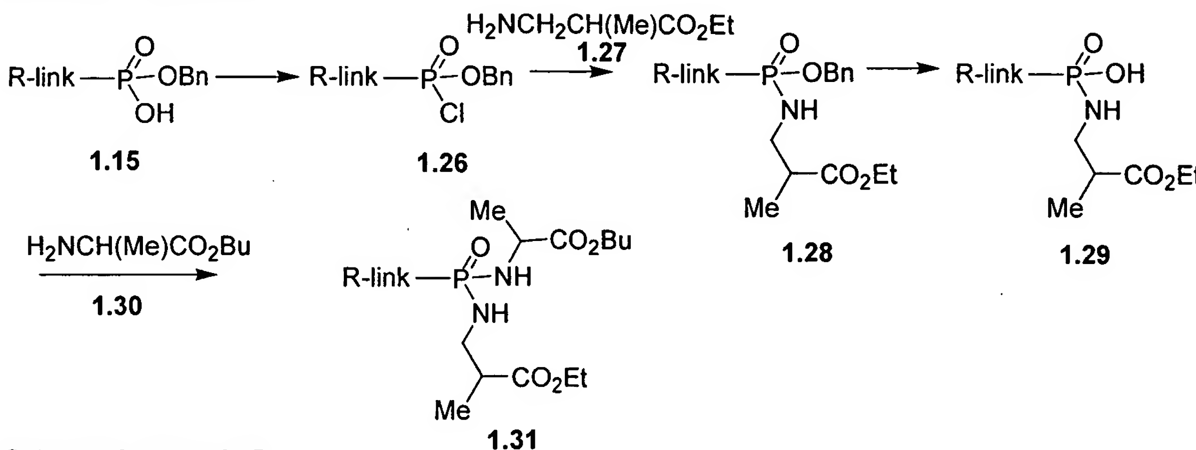
Scheme 1 Example 2



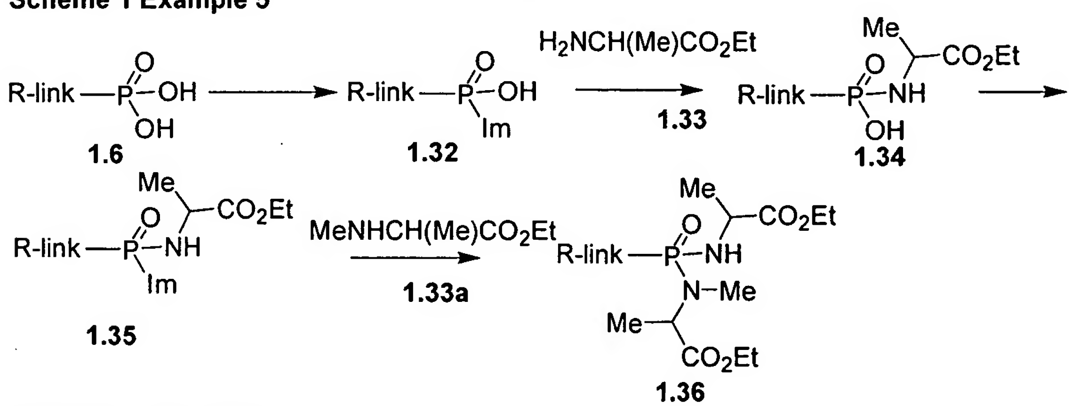
Scheme 1 Example 3



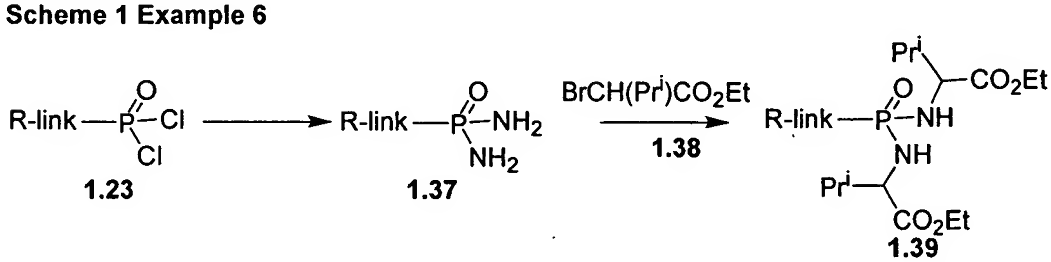
Scheme 1 Example 4



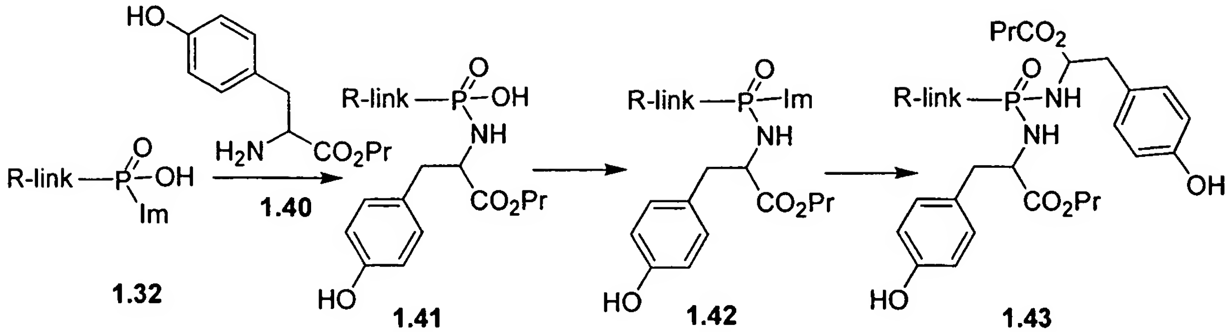
Scheme 1 Example 5



Scheme 1 Example 6



Scheme 1 Example 7



1.32 1.41 1.42 1.43

Scheme **2** illustrates methods for the preparation of phosphonate monoamidates.

In one procedure, a phosphonate monoester **1.1** is converted, as described in Scheme **1**, into the activated derivative **1.8**. This compound is then reacted, as described above, with an aminoester **1.9**, in the presence of a base, to afford the monoamidate product **2.1**.

The procedure is illustrated in Scheme **2**, Example **1**. In this method, a monophenyl phosphonate **2.7** is reacted with, for example, thionyl chloride, as described in *J. Gen. Chem. USSR*., 1983, 32, 367, to give the chloro product **2.8**. The product is then reacted, as described in Scheme **1**, with ethyl alaninate **2.9**, to yield the amidate **2.10**.

Using the above procedures, but employing, in place of ethyl alaninate **2.9**, different aminoesters **1.9**, the corresponding products **2.1** are obtained.

Alternatively, the phosphonate monoester **1.1** is coupled, as described in Scheme **1**, with an aminoester **1.9** to produce the amidate **2.1**. If necessary, the R^1 substituent is then altered, by initial cleavage to afford the phosphonic acid **2.2**. The procedures for this transformation depend on the nature of the R^1 group, and are described above. The phosphonic acid is then transformed into the ester amidate product **2.3**, by reaction with the hydroxy compound R^3OH, in which the group R^3 is aryl, heteroaryl, alkyl, cycloalkyl, haloalkyl etc, using the same coupling procedures (carbodiimide, Aldrithiol-2, PYBOP, Mitsonobu reaction etc) described in Scheme **1** for the coupling of amines and phosphonic acids.

Examples of this method are shown in Scheme **2**, Examples and **2** and **3**. In the sequence shown in Example **2**, a monobenzyl phosphonate **2.11** is transformed by reaction with ethyl alaninate, using one of the methods described above, into the monoamidate **2.12**. The benzyl group is then removed by catalytic hydrogenation in ethyl acetate solution over a 5% palladium on carbon catalyst, to afford the phosphonic acid amidate **2.13**. The product is then reacted in

dichloromethane solution at ambient temperature with equimolar amounts of 1-(dimethylaminopropyl)-3-ethylcarbodiimide and trifluoroethanol **2.14**, for example as described in *Tetrahedron Lett.*, 2001, 42, 8841, to yield the amidate ester **2.15**.

In the sequence shown in Scheme **2**, Example **3**, the monoamidate **2.13** is coupled, in tetrahydrofuran solution at ambient temperature, with equimolar amounts of dicyclohexyl carbodiimide and 4-hydroxy-N-methylpiperidine **2.16**, to produce the amidate ester product **2.17**.

Using the above procedures, but employing, in place of the ethyl alaninate product **2.12** different monoacids **2.2**, and in place of trifluoroethanol **2.14** or 4-hydroxy-N-methylpiperidine **2.16**, different hydroxy compounds R^3OH, the corresponding products **2.3** are obtained.

Alternatively, the activated phosphonate ester **1.8** is reacted with ammonia to yield the amidate **2.4**. The product is then reacted, as described in Scheme **1**, with a haloester **2.5**, in the presence of a base, to produce the amidate product **2.6**. If appropriate, the nature of the R^1 group is changed, using the procedures described above, to give the product **2.3**. The method is illustrated in Scheme **2**, Example **4**. In this sequence, the monophenyl phosphoryl chloride **2.18** is reacted, as described in Scheme **1**, with ammonia, to yield the amino product **2.19**. This material is then reacted in N-methylpyrrolidinone solution at 170°C with butyl 2-bromo-3-phenylpropionate **2.20** and potassium carbonate, to afford the amidate product **2.21**.

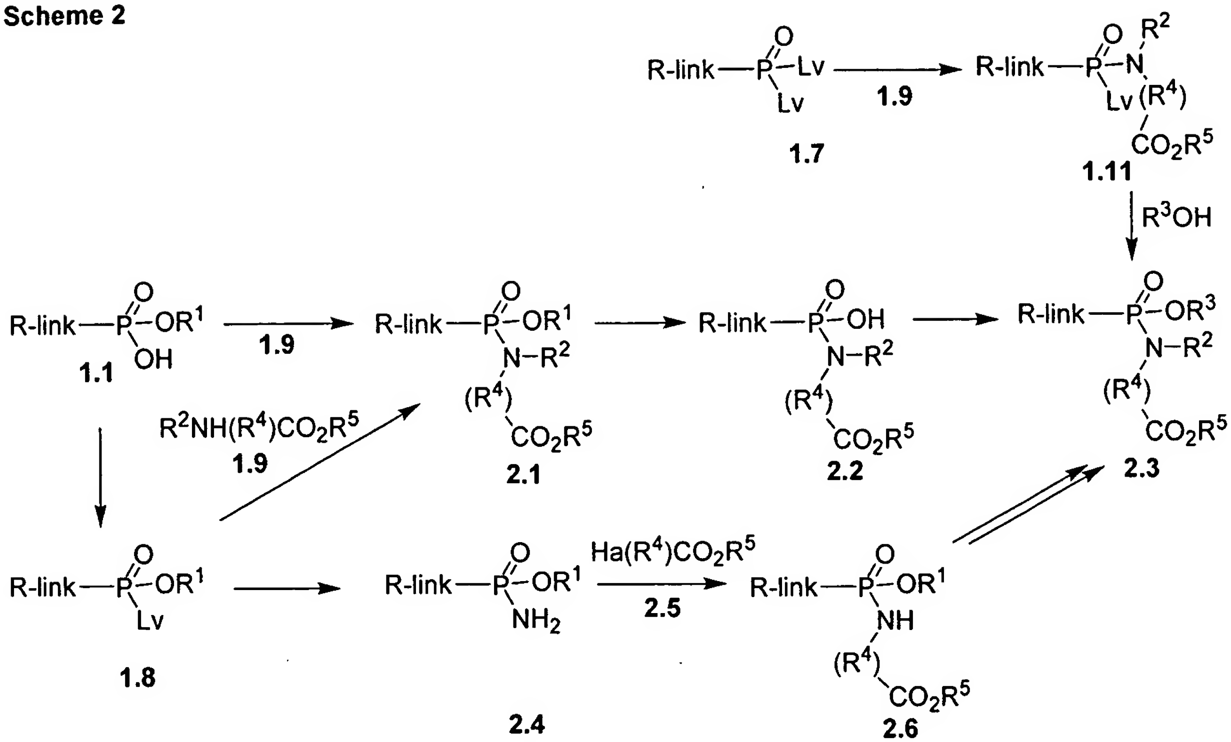
Using these procedures, but employing, in place of butyl 2-bromo-3-phenylpropionate **2.20**, different haloesters **2.5**, the corresponding products **2.6** are obtained.

The monoamidate products **2.3** are also prepared from the doubly activated phosphonate derivatives **1.7**. In this procedure, examples of which are described in *Syn. Lett.*, 1998, 1, 73, the intermediate **1.7** is reacted with a limited amount of the aminoester **1.9** to give the mono-displacement product **1.11**. The latter compound is then reacted with the hydroxy compound R^3OH in a polar organic solvent such as dimethylformamide, in the presence of a base such as diisopropylethylamine, to yield the monoamidate ester **2.3**.

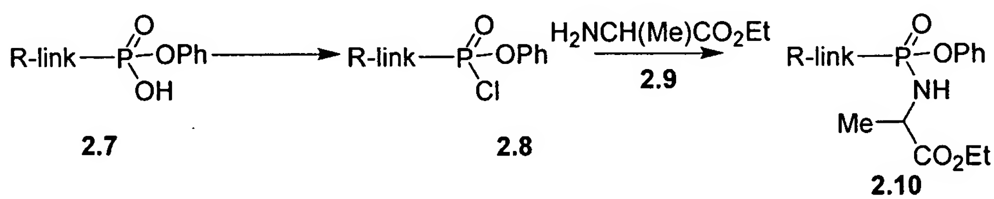
The method is illustrated in Scheme **2**, Example **5**. In this method, the phosphoryl dichloride **2.22** is reacted in dichloromethane solution with one molar equivalent of ethyl N-methyl tyrosinate **2.23** and dimethylaminopyridine, to generate the monoamidate **2.24**. The product is then reacted with phenol **2.25** in dimethylformamide containing potassium carbonate, to yield the ester amidate product **2.26**.

Using these procedures, but employing, in place of ethyl N-methyl tyrosinate **2.23** or phenol **2.25**, the aminoesters **1.9** and/or the hydroxy compounds R^3OH, the corresponding products **2.3** are obtained.

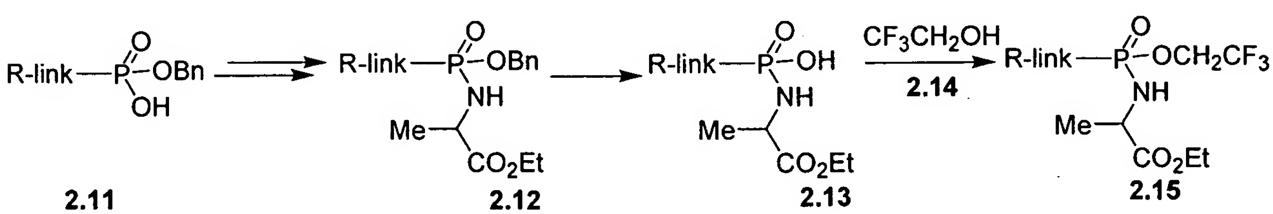
Scheme 2



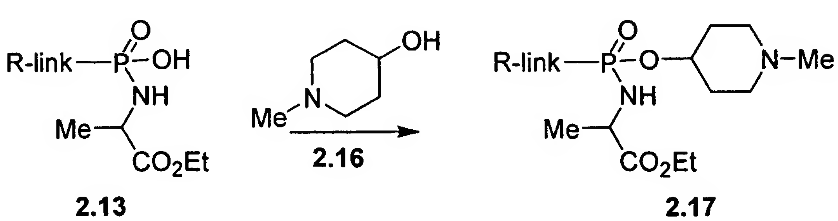
Scheme 2 Example 1



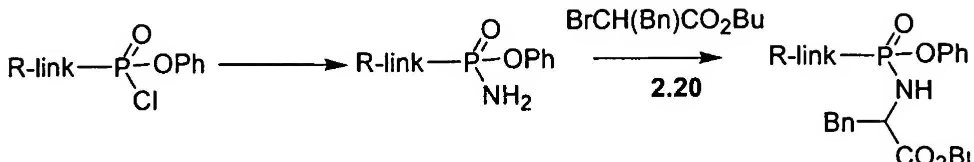
Scheme 2 Example 2



Scheme 2 Example 3

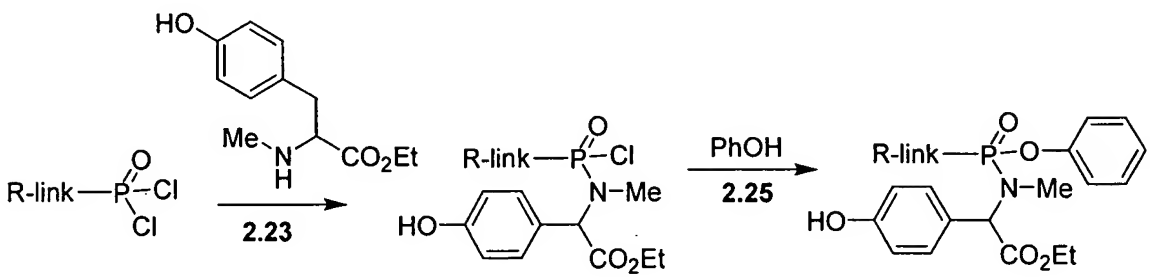


Scheme 2 Example 4



2.18 2.19 2.21

Scheme 2 Example 5



2.22 2.24 2.26

Scheme **3** illustrates methods for the preparation of carboalkoxy-substituted phosphonate diesters in which one of the ester groups incorporates a carboalkoxy substituent.

In one procedure, a phosphonate monoester **1.1**, prepared as described above, is coupled, using one of the methods described above, with a hydroxyester **3.1**, in which the groups R^4 and R^5 are as described in Scheme **1**. For example, equimolar amounts of the reactants are coupled in the presence of a carbodiimide such as dicyclohexyl carbodiimide, as described in Aust. J. Chem., 1963, 609, optionally in the presence of dimethylaminopyridine, as described in *Tetrahedron Lett.*, 1999, 55, 12997. The reaction is conducted in an inert solvent at ambient temperature.

The procedure is illustrated in Scheme **3**, Example **1**. In this method, a monophenyl phosphonate **3.9** is coupled, in dichloromethane solution in the presence of dicyclohexyl carbodiimide, with ethyl 3-hydroxy-2-methylpropionate **3.10** to yield the phosphonate mixed diester **3.11**.

Using this procedure, but employing, in place of ethyl 3-hydroxy-2-methylpropionate **3.10**, different hydroxyesters **3.1**, the corresponding products **3.2** are obtained.

The conversion of a phosphonate monoester **1.1** into a mixed diester **3.2** is also accomplished by means of a Mitsonobu coupling reaction with the hydroxyester **3.1**, as

described in *Org. Lett.*, 2001, 643. In this method, the reactants **1.1** and **3.1** are combined in a polar solvent such as tetrahydrofuran, in the presence of a triarylphosphine and a dialkyl azodicarboxylate, to give the mixed diester **3.2**. The R^1 substituent is varied by cleavage, using the methods described previously, to afford the monoacid product **3.3**. The product is then coupled, for example using methods described above, with the hydroxy compound R^3OH, to give the diester product **3.4**.

The procedure is illustrated in Scheme **3**, Example **2**. In this method, a monoallyl phosphonate **3.12** is coupled in tetrahydrofuran solution, in the presence of triphenylphosphine and diethylazodicarboxylate, with ethyl lactate **3.13** to give the mixed diester **3.14**. The product is reacted with tris(triphenylphosphine) rhodium chloride (Wilkinson catalyst) in acetonitrile, as described previously, to remove the allyl group and produce the monoacid product **3.15**. The latter compound is then coupled, in pyridine solution at ambient temperature, in the presence of dicyclohexyl carbodiimide, with one molar equivalent of 3-hydroxypyridine **3.16** to yield the mixed diester **3.17**.

Using the above procedures, but employing, in place of the ethyl lactate **3.13** or 3-hydroxypyridine, a different hydroxyester **3.1** and/or a different hydroxy compound R^3OH, the corresponding products **3.4** are obtained.

The mixed diesters **3.2** are also obtained from the monoesters **1.1** via the intermediacy of the activated monoesters **3.5**. In this procedure, the monoester **1.1** is converted into the activated compound **3.5** by reaction with, for example, phosphorus pentachloride, as described in *J. Org. Chem.*, 2001, 66, 329, or with thionyl chloride or oxalyl chloride (Lv = Cl), or with triisopropylbenzenesulfonyl chloride in pyridine, as described in *Nucleosides and Nucleotides*, 2000, 19, 1885, or with carbonyl diimidazole, as described in *J. Med. Chem.*, 2002, 45, 1284. The resultant activated monoester is then reacted with the hydroxyester **3.1**, as described above, to yield the mixed diester **3.2**.

The procedure is illustrated in Scheme **3**, Example **3**. In this sequence, a monophenyl phosphonate **3.9** is reacted, in acetonitrile solution at 70°C, with ten equivalents of thionyl chloride, so as to produce the phosphoryl chloride **3.19**. The product is then reacted with ethyl 4-carbamoyl-2-hydroxybutyrate **3.20** in dichloromethane containing triethylamine, to give the mixed diester **3.21**.

Using the above procedures, but employing, in place of ethyl 4-carbamoyl-2-hydroxybutyrate **3.20**, different hydroxyesters **3.1**, the corresponding products **3.2** are obtained.

The mixed phosphonate diesters are also obtained by an alternative route for incorporation of the R^3O group into intermediates **3.3** in which the hydroxyester moiety is already incorporated. In this procedure, the monoacid intermediate **3.3** is converted into the activated derivative **3.6** in which Lv is a leaving group such as chloro, imidazole, and the like, as previously described. The activated intermediate is then reacted with the hydroxy compound R^3OH, in the presence of a base, to yield the mixed diester product **3.4**.

The method is illustrated in Scheme **3**, Example **4**. In this sequence, the phosphonate monoacid **3.22** is reacted with trichloromethanesulfonyl chloride in tetrahydrofuran containing collidine, as described in *J. Med. Chem.*, 1995, 38, 4648, to produce the trichloromethanesulfonyloxy product **3.23**. This compound is reacted with 3-(morpholinomethyl)phenol **3.24** in dichloromethane containing triethylamine, to yield the mixed diester product **3.25**.

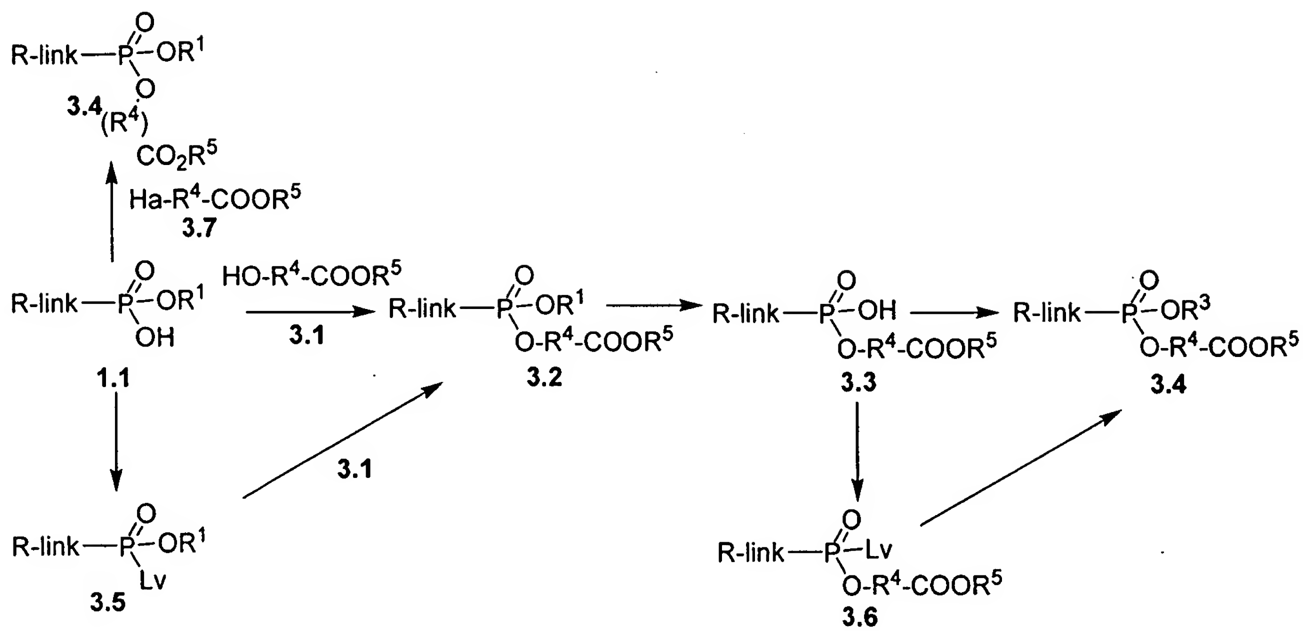
Using the above procedures, but employing, in place of with 3-(morpholinomethyl)phenol **3.24**, different carbinols R^3OH, the corresponding products **3.4** are obtained.

The phosphonate esters **3.4** are also obtained by means of alkylation reactions performed on the monoesters **1.1**. The reaction between the monoacid **1.1** and the haloester **3.7** is performed in a polar solvent in the presence of a base such as diisopropylethylamine, as described in *Anal. Chem.*, 1987, 59, 1056, or triethylamine, as described in *J. Med. Chem.*, 1995, 38, 1372, or in a non-polar solvent such as benzene, in the presence of 18-crown-6, as described in *Syn. Comm.*, 1995, 25, 3565.

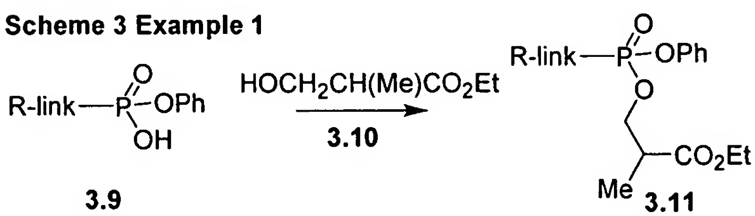
The method is illustrated in Scheme **3**, Example **5**. In this procedure, the monoacid **3.26** is reacted with ethyl 2-bromo-3-phenylpropionate **3.27** and diisopropylethylamine in dimethylformamide at 80°C to afford the mixed diester product **3.28**.

Using the above procedure, but employing, in place of ethyl 2-bromo-3-phenylpropionate **3.27**, different haloesters **3.7**, the corresponding products **3.4** are obtained.

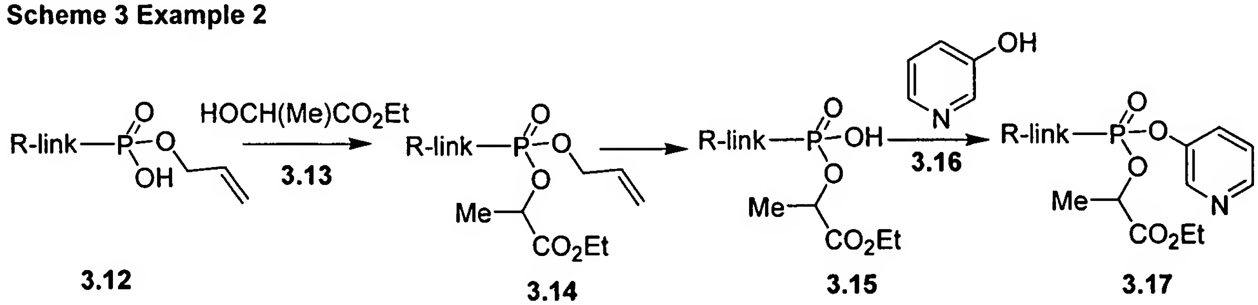
Scheme 3



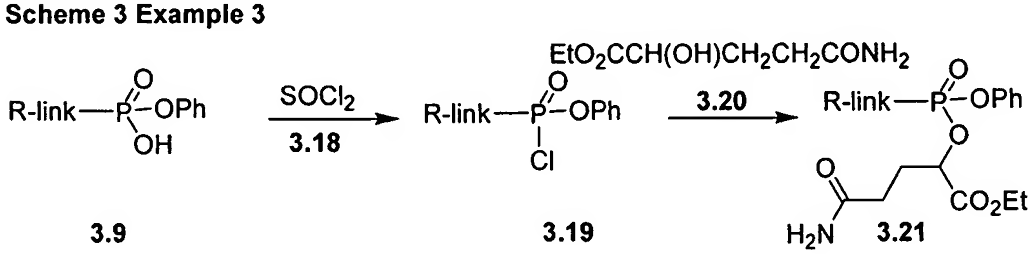
Scheme 3 Example 1



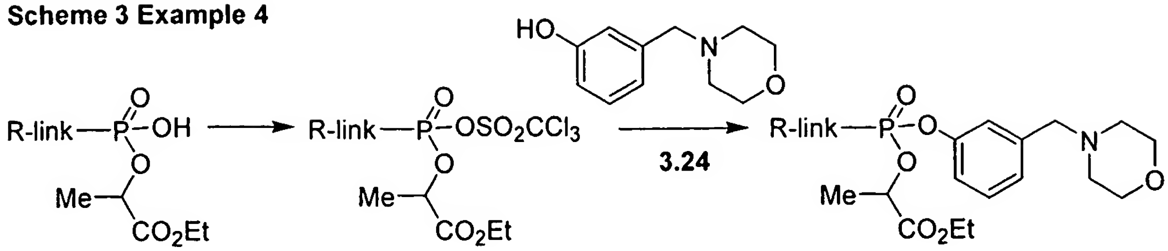
Scheme 3 Example 2



Scheme 3 Example 3

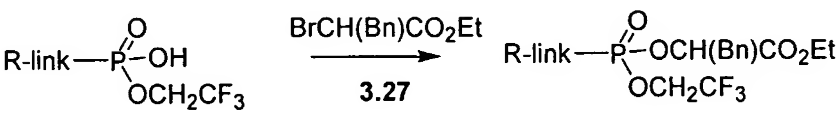


Scheme 3 Example 4



3.22 3.23 3.25

Scheme 3 Example 5



3.26 3.28

Scheme 4 illustrates methods for the preparation of phosphonate diesters in which both the ester substituents incorporate carboalkoxy groups.

The compounds are prepared directly or indirectly from the phosphonic acids **1.6**. In one alternative, the phosphonic acid is coupled with the hydroxyester **4.2**, using the conditions described previously in Schemes **1** - **3**, such as coupling reactions using dicyclohexyl carbodiimide or similar reagents, or under the conditions of the Mitsonobu reaction, to afford the diester product **4.3** in which the ester substituents are identical.

This method is illustrated in Scheme **4**, Example **1**. In this procedure, the phosphonic acid **1.6** is reacted with three molar equivalents of butyl lactate **4.5** in the presence of Aldrithiol-2 and triphenyl phosphine in pyridine at ca. 70°C, to afford the diester **4.6**.

Using the above procedure, but employing, in place of butyl lactate **4.5**, different hydroxyesters **4.2**, the corresponding products **4.3** are obtained.

Alternatively, the diesters **4.3** are obtained by alkylation of the phosphonic acid **1.6** with a haloester **4.1**. The alkylation reaction is performed as described in Scheme **3** for the preparation of the esters **3.4**.

This method is illustrated in Scheme **4**, Example **2**. In this procedure, the phosphonic acid **1.6** is reacted with excess ethyl 3-bromo-2-methylpropionate **4.7** and diisopropylethylamine

in dimethylformamide at ca. 80°C, as described in Anal. Chem., 1987, 59, 1056, to produce the diester **4.8**.

Using the above procedure, but employing, in place of ethyl 3-bromo-2-methylpropionate **4.7**, different haloesters **4.1**, the corresponding products **4.3** are obtained.

The diesters **4.3** are also obtained by displacement reactions of activated derivatives **1.7** of the phosphonic acid with the hydroxyesters **4.2**. The displacement reaction is performed in a polar solvent in the presence of a suitable base, as described in Scheme **3**. The displacement reaction is performed in the presence of an excess of the hydroxyester, to afford the diester product **4.3** in which the ester substituents are identical, or sequentially with limited amounts of different hydroxyesters, to prepare diesters **4.3** in which the ester substituents are different.

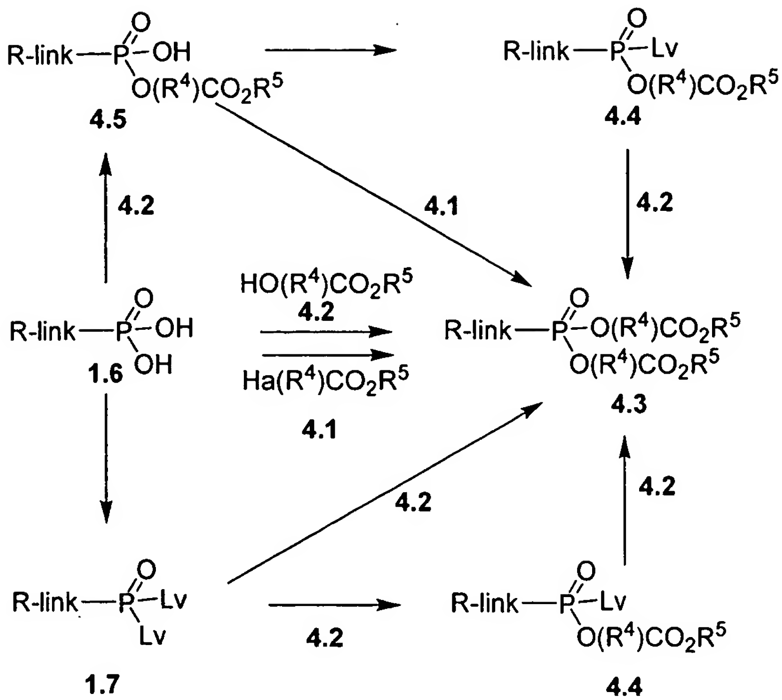
The methods are illustrated in Scheme **4**, Examples **3** and **4**. As shown in Example **3**, the phosphoryl dichloride **2.22** is reacted with three molar equivalents of ethyl 3-hydroxy-2-(hydroxymethyl)propionate **4.9** in tetrahydrofuran containing potassium carbonate, to obtain the diester product **4.10**.

Using the above procedure, but employing, in place of ethyl 3-hydroxy-2-(hydroxymethyl)propionate **4.9**, different hydroxyesters **4.2**, the corresponding products **4.3** are obtained.

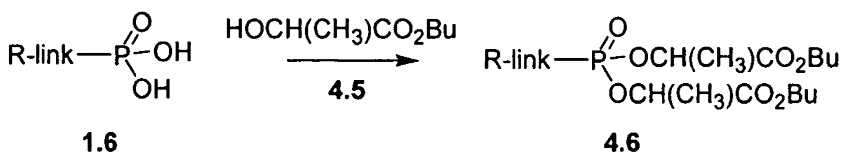
Scheme **4**, Example **4** depicts the displacement reaction between equimolar amounts of the phosphoryl dichloride **2.22** and ethyl 2-methyl-3-hydroxypropionate **4.11**, to yield the monoester product **4.12**. The reaction is conducted in acetonitrile at 70°C in the presence of diisopropylethylamine. The product **4.12** is then reacted, under the same conditions, with one molar equivalent of ethyl lactate **4.13**, to give the diester product **4.14**.

Using the above procedures, but employing, in place of ethyl 2-methyl-3-hydroxypropionate **4.11** and ethyl lactate **4.13**, sequential reactions with different hydroxyesters **4.2**, the corresponding products **4.3** are obtained.

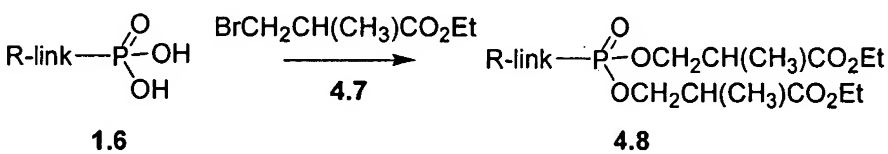
Scheme 4



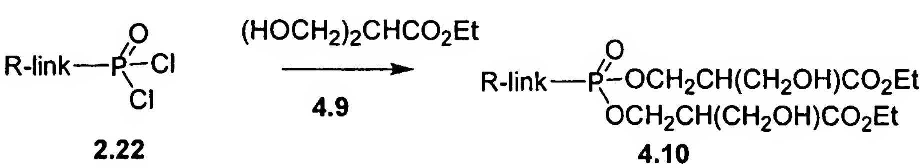
Scheme 4 Example 1



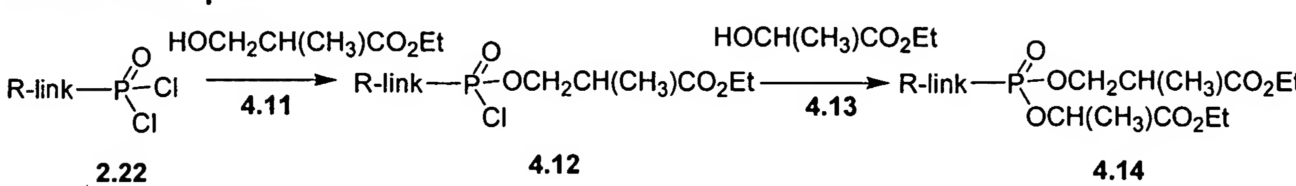
Scheme 4 Example 2



Scheme 4 Example 3



Scheme 4 Example 4



Aryl halides undergo Ni^{+2} catalyzed reaction with phosphite derivatives to give aryl phosphonate containing compounds (Balthazar, *et al.* (1980) *J. Org. Chem.* 45:5425). Phosphonates may also be prepared from the chlorophosphonate in the presence of a palladium catalyst using aromatic triflates (Petrakis, *et al.*, (1987) *J. Am. Chem. Soc.*109:2831; Lu, *et al.*, (1987) *Synthesis*, 726). In another method, aryl phosphonate esters are prepared from aryl phosphates under anionic rearrangement conditions (Melvin (1981) *Tetrahedron Lett.* 22:3375; Casteel, *et al.*, (1991) *Synthesis*, 691). N-Alkoxy aryl salts with alkali metal derivatives of cyclic alkyl phosphonate provide general synthesis for heteroaryl-2-phosphonate linkers (Redmore (1970) *J. Org. Chem.* 35:4114). These above mentioned methods can also be extended to compounds where the W^5 group is a heterocycle. Cyclic-1,3-propanyl prodrugs of phosphonates are also synthesized from phosphonic diacids and substituted propane-1,3-diols using a coupling reagent such as 1,3-dicyclohexylcarbodiimide (DCC) in presence of a base (*e.g.*, pyridine). Other carbodiimide based coupling agents like 1,3-disopropylcarbodiimide or water soluble reagent, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) can also be utilized for the synthesis of cyclic phosphonate prodrugs.

The carbamoyl group may be formed by reaction of a hydroxy group according to the methods known in the art, including the teachings of Ellis, US 2002/0103378 A1 and Hajima, US Patent No. 6018049.

Generally, the reaction conditions such as temperature, reaction time, solvents, work-up procedures, and the like, will be those common in the art for the particular reaction to be performed. The cited reference material, together with material cited therein, contains detailed descriptions of such conditions. Typically the temperatures will be -100°C to 200°C, solvents will be aprotic or protic, and reaction times will be 10 seconds to 10 days. Work-up typically consists of quenching any unreacted reagents followed by partition between a water/organic layer system (extraction) and separating the layer containing the product.

Oxidation and reduction reactions are typically carried out at temperatures near room temperature (about 20°C), although for metal hydride reductions frequently the temperature is reduced to 0°C to -100°C, solvents are typically aprotic for reductions and may be either protic or aprotic for oxidations. Reaction times are adjusted to achieve desired conversions.

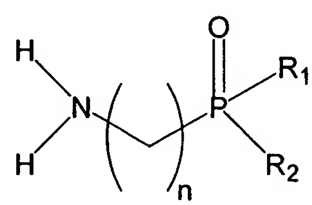
Condensation reactions are typically carried out at temperatures near room temperature,

although for non-equilibrating, kinetically controlled condensations reduced temperatures (0°C to -100°C) are also common. Solvents can be either protic (common in equilibrating reactions) or aprotic (common in kinetically controlled reactions).

Standard synthetic techniques such as azeotropic removal of reaction by-products and use of anhydrous reaction conditions (*e.g.*, inert gas environments) are common in the art and will be applied when applicable.

General synthetic routes to substituted imidazoles are well established. See Ogata M (1988) *Annals of the New York Academy of Sciences* 544:12-31; Takahashi *et al.* (1985) *Heterocycles* 23:6, 1483-1492; Ogata *et al.* (1980) *CHEM IND LONDON* 2:5-86; Yanagisawa *et al.* US Patent No. 5646171; Rachwal *et al.* US 2002/0115693 A1; Carlson *et al.* US Patent Nos. 3790593; 3761491 and 3773781; Aono *et al.* US Patent No. 6054591; Hajima *et al.* US Patent No. 6057448; Sugimoto *et al.* EP 00552060 and US Patent No. 5326780.

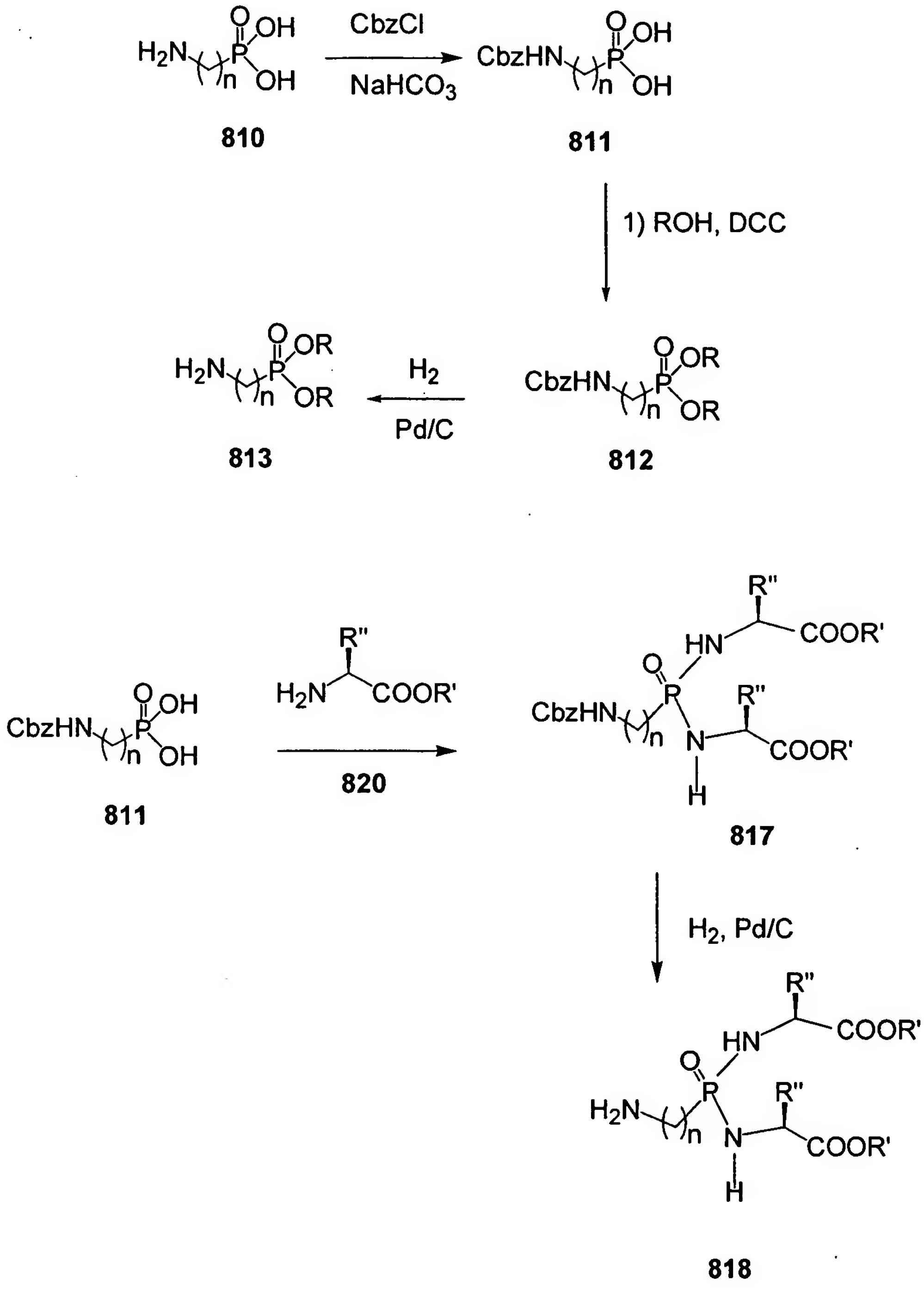
Amino alkyl phosphonate compounds **809**:



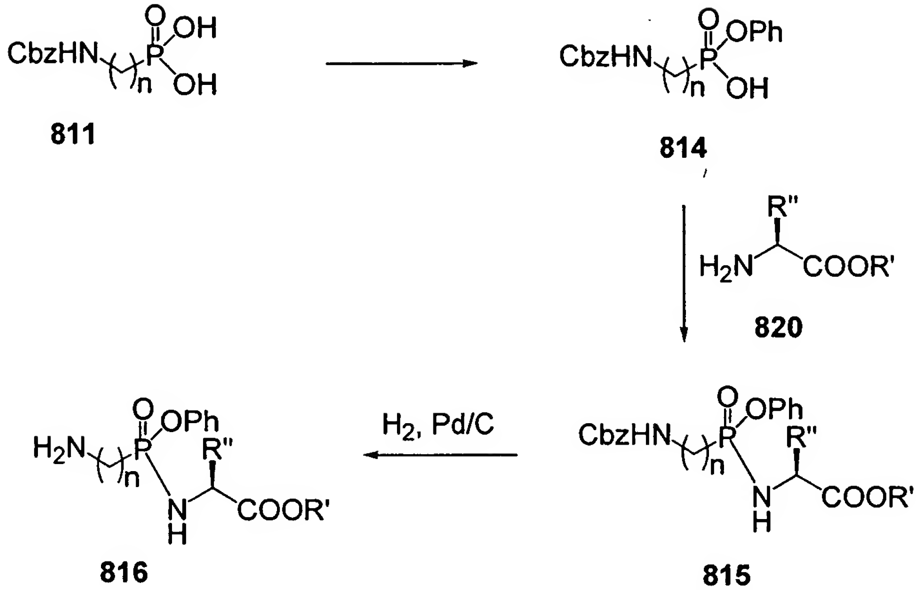
809

are a generic representative of compounds **811, 813, 814, 816** and **818** (Scheme X2). The alkylene chain may be any length from 1 to 18 methylene groups (n = 1-18). Commercial amino phosphonic acid **810** was protected as carbamate **811**. The phosphonic acid **811** was converted to phosphonate **812** upon treatment with ROH in the presence of DCC or other conventional coupling reagents. Coupling of phosphonic acid **811** with esters of amino acid **820** provided bisamidate **817**. Conversion of acid **811** to bisphenyl phosphonate followed by hydrolysis gave mono-phosphonic acid **814** (Cbz = $C_6H_5CH_2C(O)$–), which was then transformed to mono-phosphonic amidate **815**. Carbamates **813, 816** and **818** were converted to their corresponding amines upon hydrogenation. Compounds **811, 813, 814, 816** and **818** are useful intermediates to form the phosphonate compounds of the invention.

Scheme X2

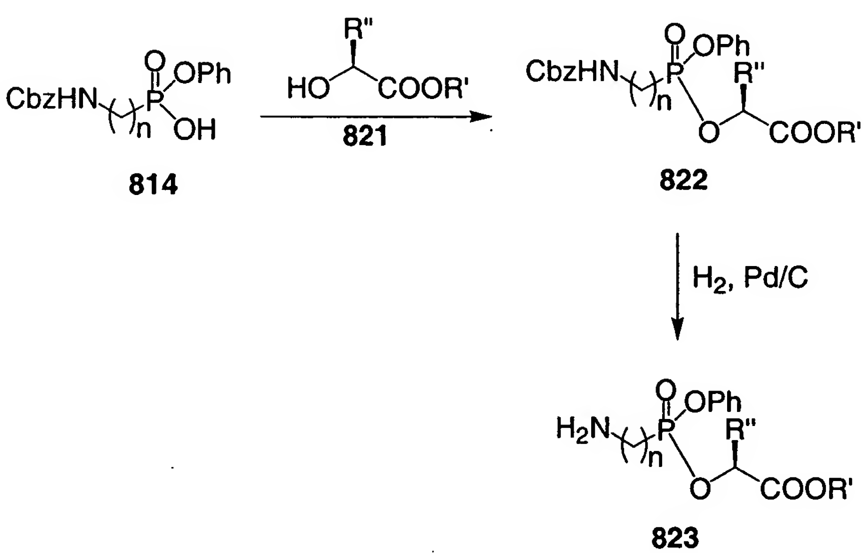


CbzCl
NaHCO3
810
811
1) ROH, DCC
H2
Pd/C
813
812
820
811
817
H2, Pd/C
818

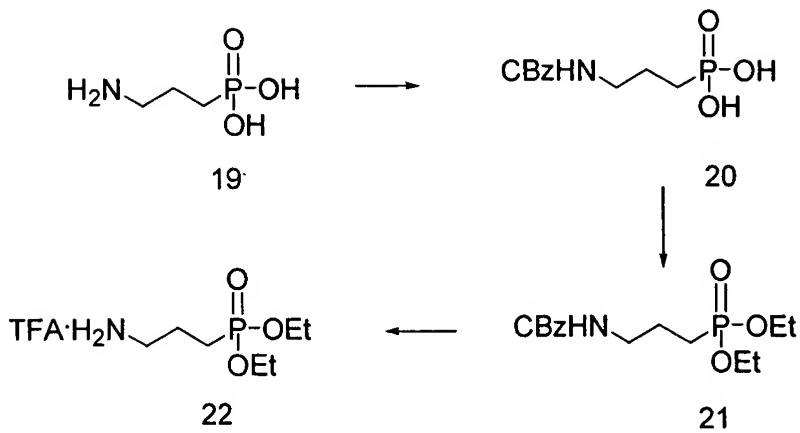


Following the similar procedures, replacement of amino acid esters **820** with lactates **821** (Scheme X3) provides mono-phosphonic lactates **823**. Lactates **823** are useful intermediates to form the phosphonate compounds of the invention.

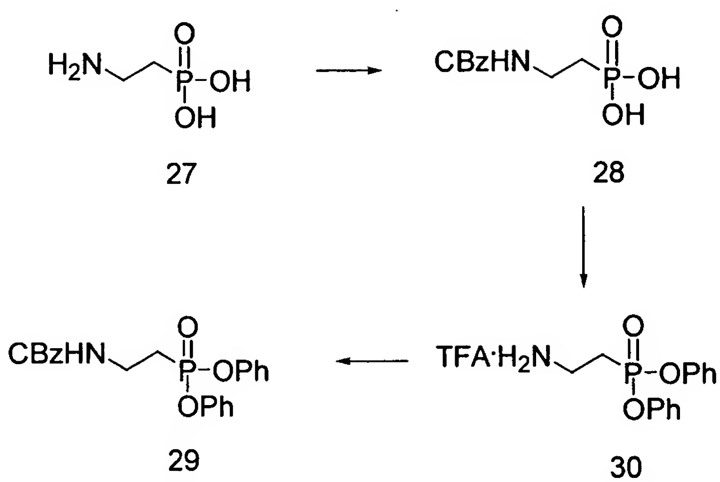
Scheme X3



Scheme X4



Scheme X5



Examples General Section

The following Examples refer to the Schemes. Some Examples have been performed multiple times. In repeated Examples, reaction conditions such as time, temperature, concentration and the like, and yields were within normal experimental ranges. In repeated Examples where significant modifications were made, these have been noted where the results varied significantly from those described. In Examples where different starting materials were used, these are noted. When the repeated Examples refer to a "corresponding" analog of a compound, such as a "corresponding ethyl ester", this intends that an otherwise present group, in this case typically a methyl ester, is taken to be the same group modified as indicated.

Example X1

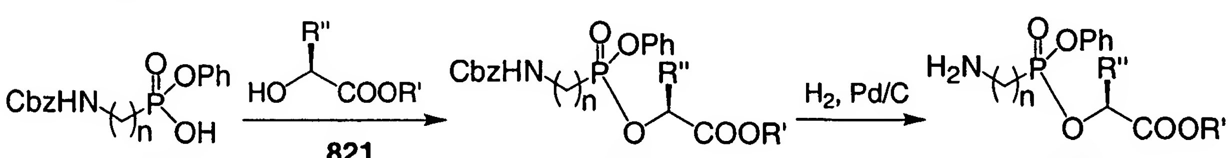
To a solution of 2-aminoethylphosphonic acid (**810** where n =2, 1.26 g, 10.1 mmol) in 2N NaOH (10.1 mL, 20.2 mmol) was added benzyl chloroformate (1.7 mL, 12.1 mmol). After the reaction mixture was stirred for 2 d at room temperature, the mixture was partitioned between Et_2O and water. The aqueous phase was acidified with 6N HCl until pH = 2. The resulting colorless solid was dissolved in MeOH (75 mL) and treated with Dowex 50WX8-200 (7 g). After the mixture was stirred for 30 minutes, it was filtered and evaporated under reduced pressure to give carbamate **28** (2.37 g, 91%) as a colorless solid.

To a solution of carbamate **28** (2.35 g, 9.1 mmol) in pyridine (40 mL) was added phenol (8.53 g, 90.6 mmol) and 1,3-dicyclohexylcarbodiimide (7.47 g, 36.2 mmol). After the reaction mixture was warmed to 70°C and stirred for 5 h, the mixture was diluted with CH_3CN and filtered. The filtrate was concentrated under reduced pressure and diluted with EtOAc. The organic phase was washed with sat. NH_4Cl, sat. $NaHCO_3$, and brine, then dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel twice (eluting 40-60% EtOAc/hexane) to give phosphonate **29** (2.13 g, 57%) as a colorless solid.

To a solution of phosphonate **29** (262 mg, 0.637 mmol) in iPrOH (5 mL) was added TFA (0.05 mL, 0.637 mmol) and 10% Pd/C (26 mg). After the reaction mixture was stirred under H_2 atmosphere (balloon) for 1 h, the mixture was filtered through Celite. The filtrate was evaporated under reduced pressure to give amine **30** (249 mg, 100%) as a colorless oil (Scheme X5).

Following the similar procedures, replacement of amino acid esters with lactates (Scheme X6) provided mono-phosphonic lactates, *e.g.*, **823**.

Scheme X6

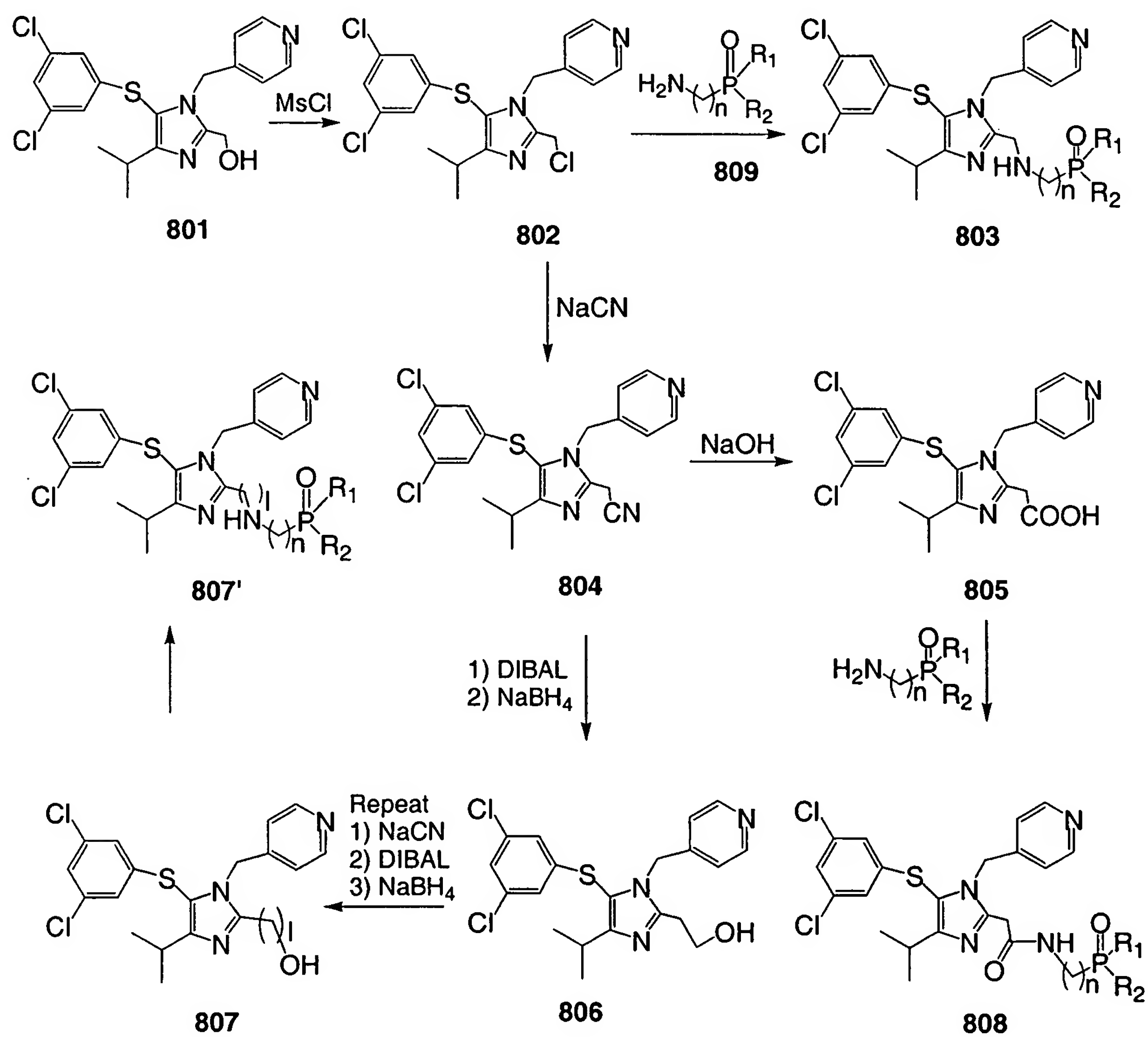


814 **822** **823**

Treatment of alcohol **801** (prepared according to literature) with MsCl and TEA afforded chloride **802** (Scheme X7). Chloride **802** was converted to compound **803** by reacting with **809**,

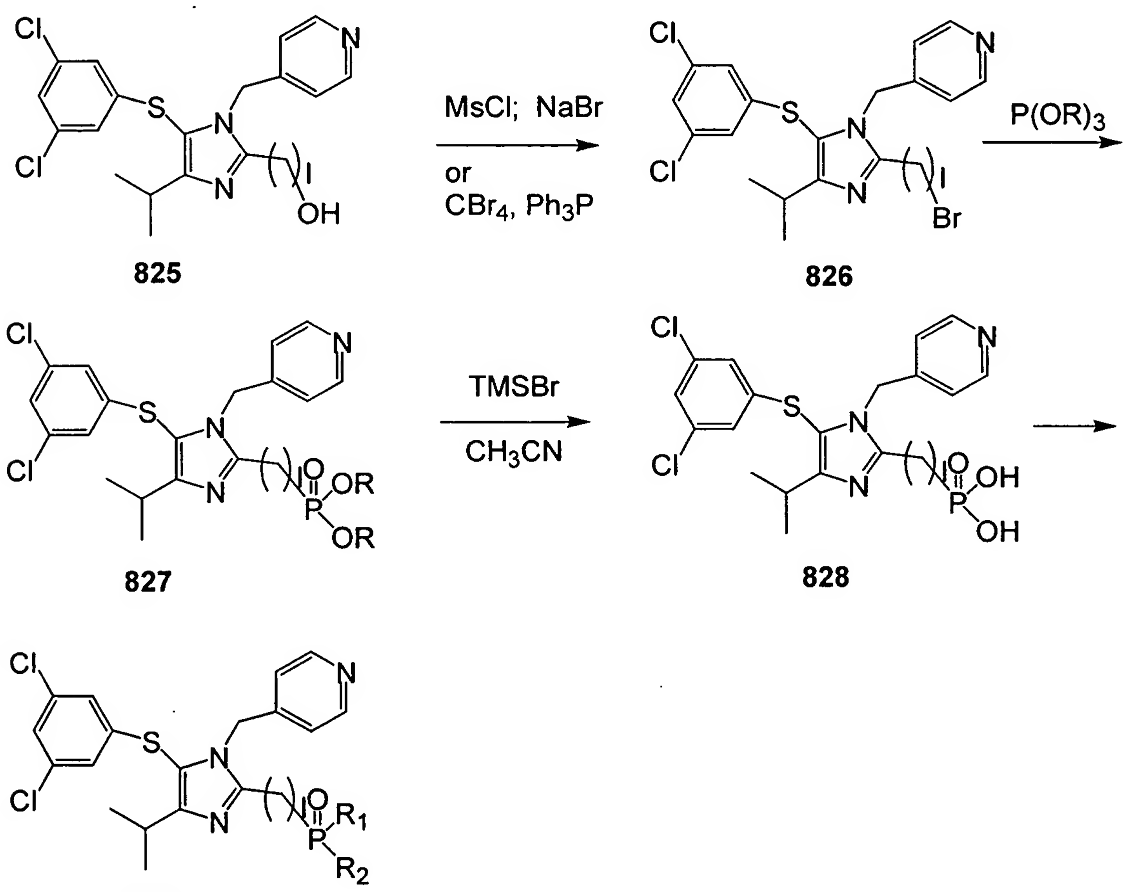
which preparation is detailed in Schemes X3 and X4, in the presence of base. When mesylate **802** was treated with NaCN, imidazole nitrile **804** was provided. Reduction of **804** with DIBAL followed by $NaBH_4$ yielded imidazole alcohol **806**. Repeating the same procedure several times furnished alcohol **807** with the desired length. Hydrolysis of imidazole nitrile **804** provided acid **805**. Coupling of acid **805** in the presence of conventional reagents afforded the amide **808**. Phosphorus compound **807'** was produced by transforming alcohol **807** to its corresponding mesylate followed by treating with amine **809**.

Scheme X7



Alcohol **825** was converted to bromide **826** by first transformed to its mesylate and then treated with NaBr, this conversion was also realized by reacting alcohol **825** with Ph_3P and CBr_4 (Scheme X8). Upon treating with $P(OR)_3$, phosphonate **827** was produced. Esters was then removed to form acid, and following the similar procedure described in Scheme X2 and X3, desired phosphonate, bisphosphoamidate, mono-phosphoamidate, and monophospholactate were produced.

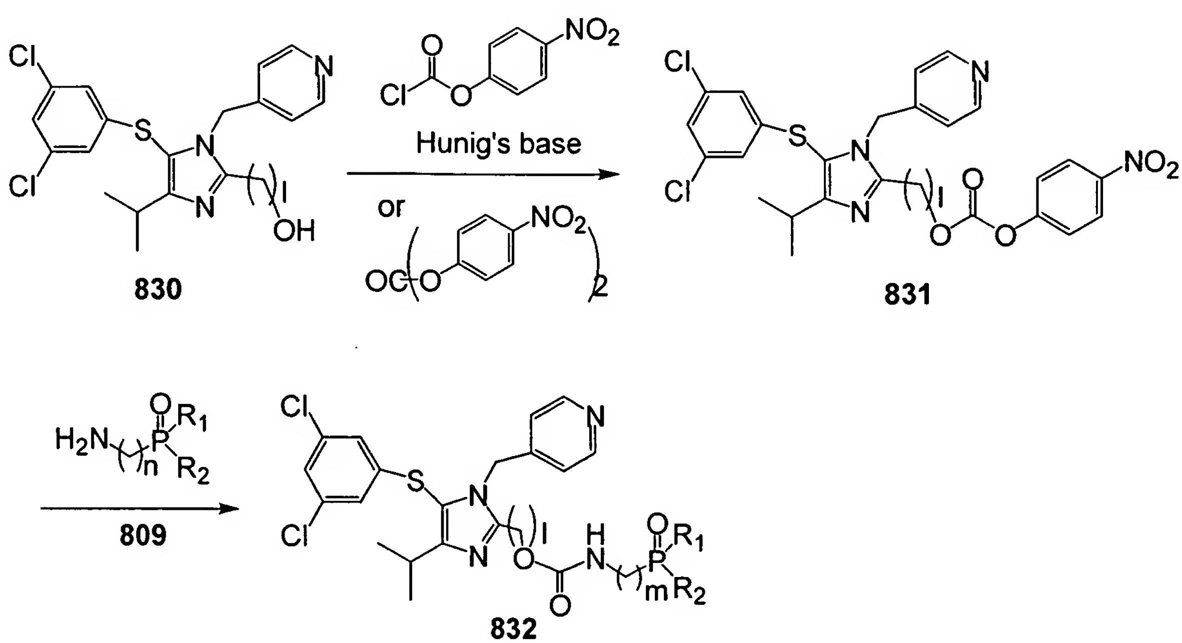
Scheme X8



825 **826** **827** **828** **829**

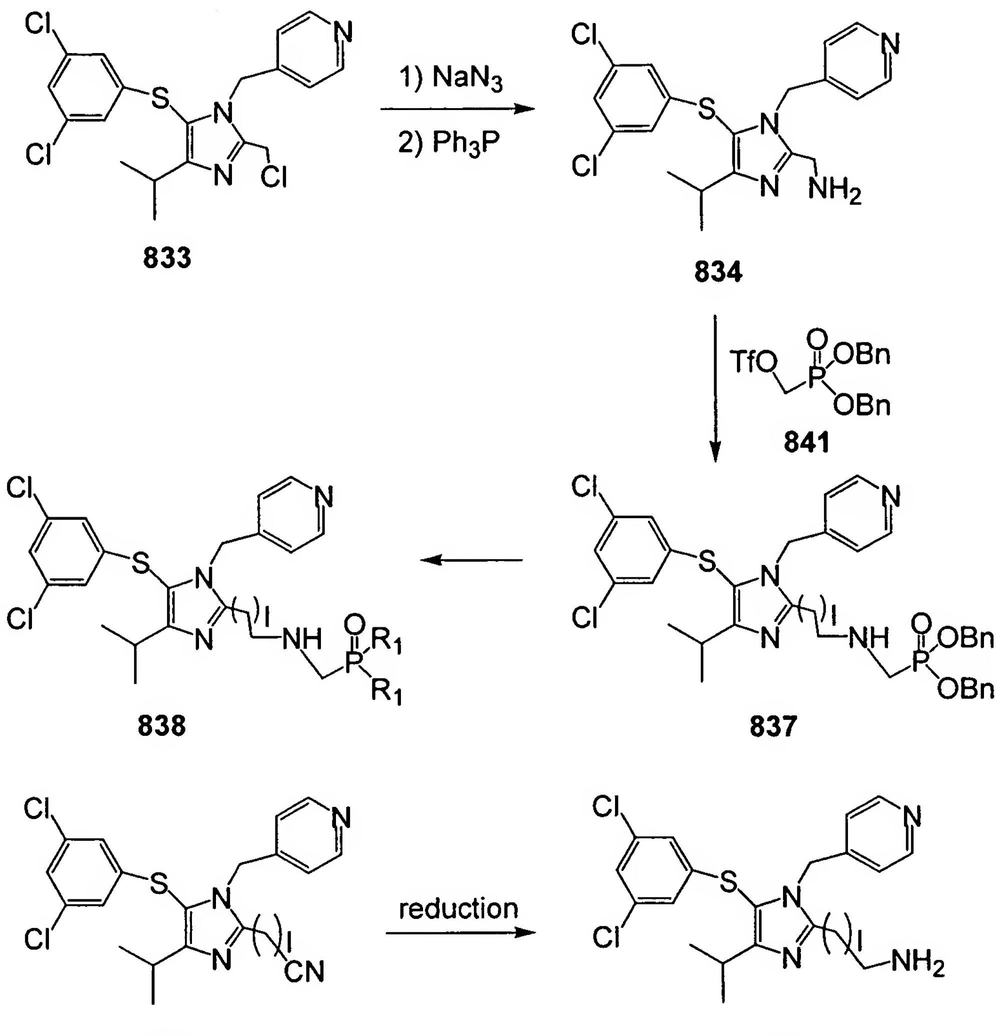
In Scheme X9, alcohol **830** was converted to carbonate **831** by reacting with either p-nitrophenyl chloroformate or p-nitrophenyl carboxy anhyride. Treatment of carbonate **831** with amine **809** in the presence of suitable base afforded desired phosphonate compounds **832**.

Scheme X9



Phosphorus compound **838** was produced according to the procedures described in Scheme X10. Replacement of chloride group in compound **833** with azide followed by reduction with triphenylphosphine provided amine **834**. Replacement of chloride group in compound **833** with cyanide, *e.g.*, sodium cyanide, provided amine **835**. Reduction of nitrile **835** furnished amine **836**. Reaction of amines, *e.g.*, **834** or **836**, with triflate **841** in the presence of a base afforded phosphonate **837**. Removal of benzyl group of **837** gave its corresponding phosphonic acid, *e.g.*, **838** where R_1 = H, which was converted to various phosphorus compounds according to the procedure described in the previous Schemes.

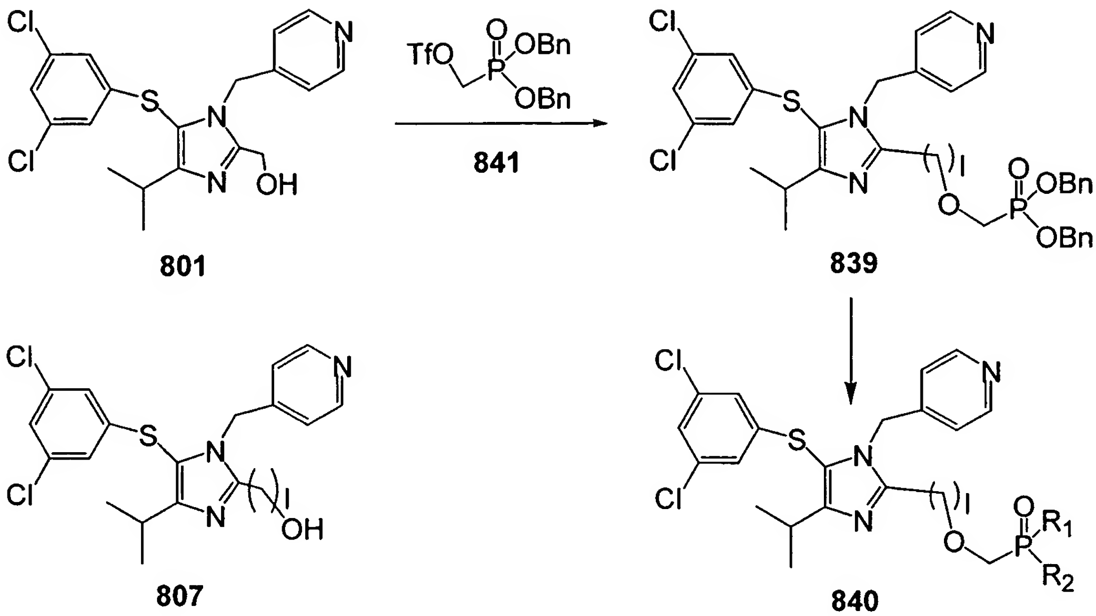
Scheme X10



833 834 837 838 835 836

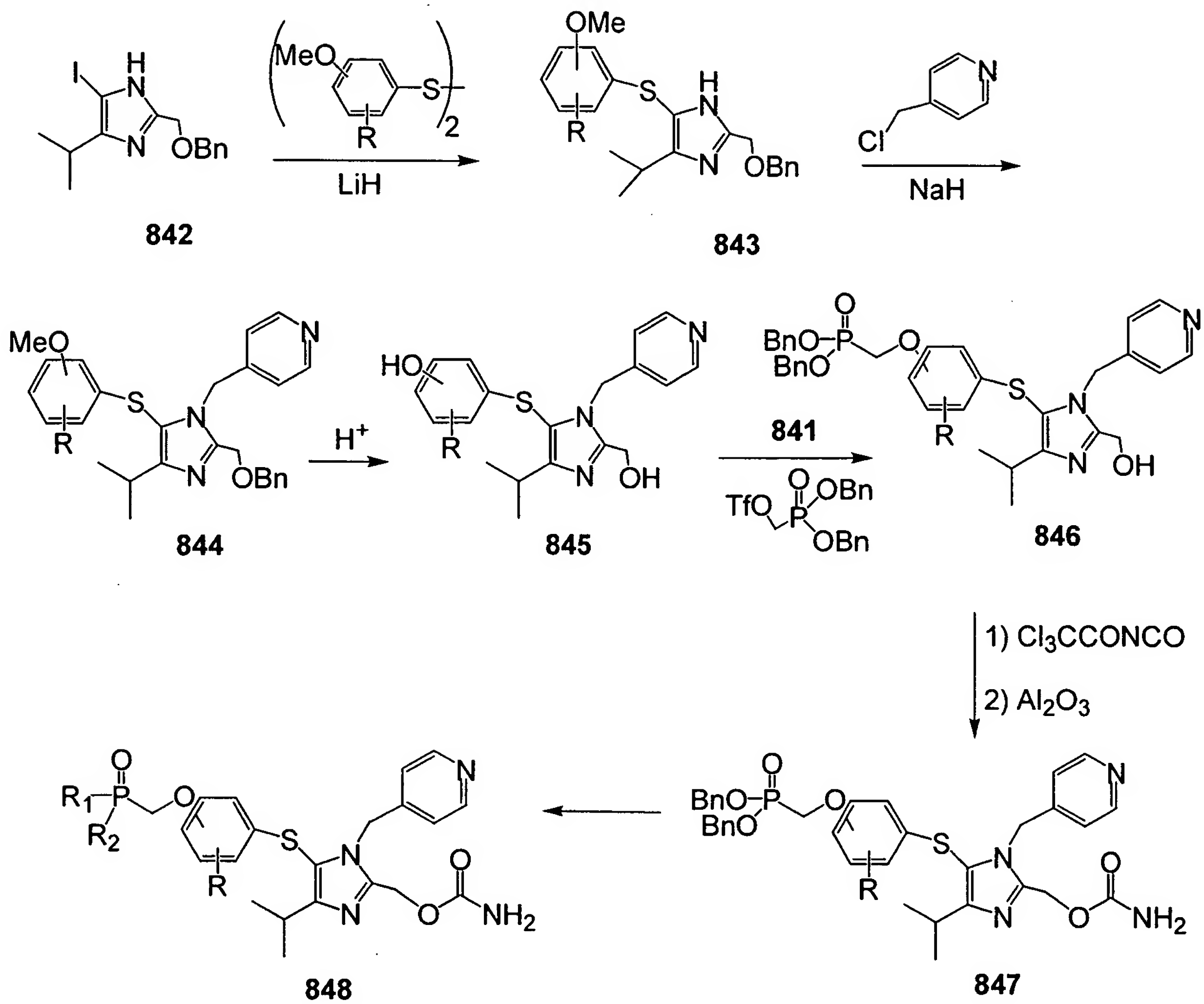
Phosphorus compound **840** was produced in a similar way as described in Scheme X10 except by replacing amines with alcohols **801**, or generally, **807** (Scheme X11).

Scheme X11



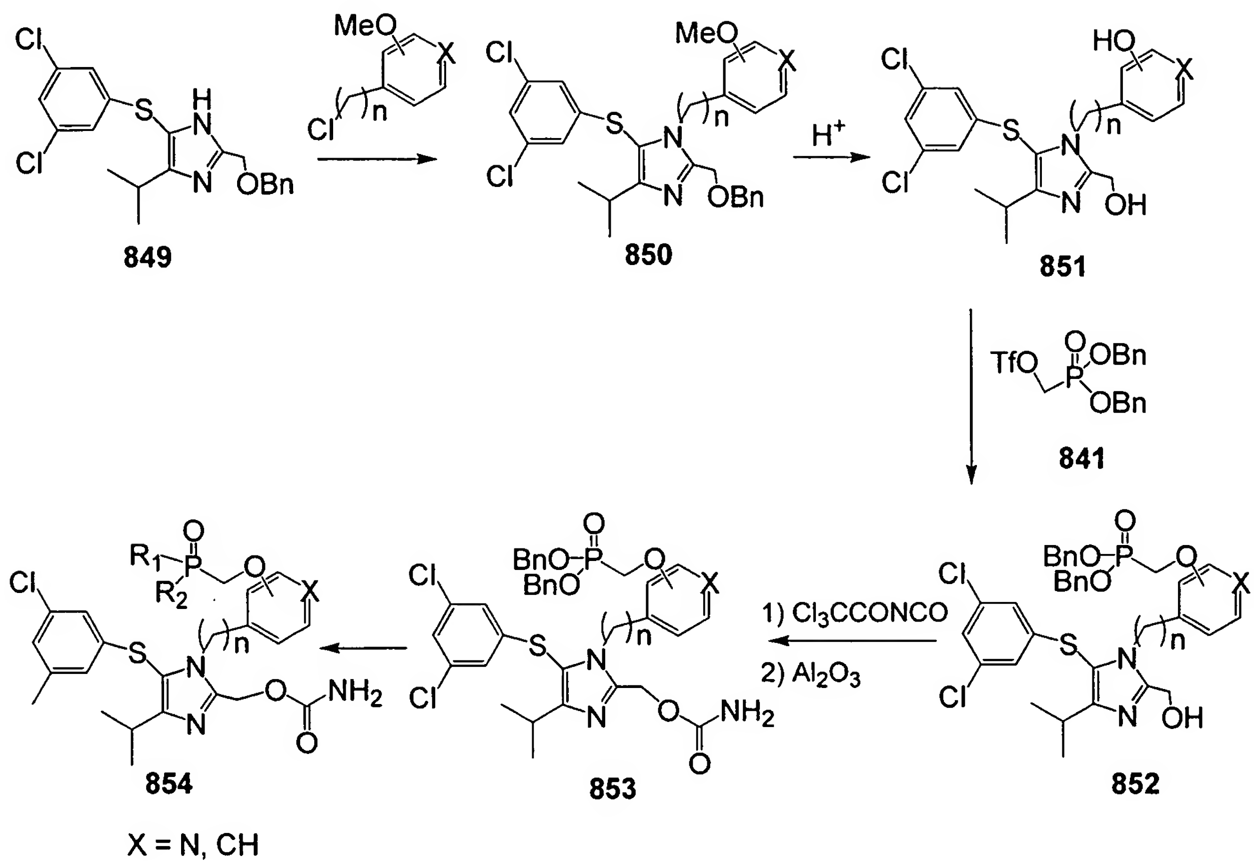
Phosphorus compound **848** was synthesized according to procedures described in Scheme X12. Iodoimidazole **842** was converted to imidazole phenyl thioether **843** by reacting with LiH and substituted phenyl disulfide (Scheme X12). Treatment of imidazole with NaH and 4-picolyl chloride gave imidazole **844**. Benzyl and methyl groups were removed by treating with strong acid to provide alcohol **845**. Conversion of phenol **845** to phosphonate **846** was accomplished by reacting phenol **845** with triflate **841** in the presence of base. Alcohol **846** was reacting with trichloroacetyl isocyanate followed by treatment of alumina afforded carbamate **847**. Phosphonate **847** was transformed to all kinds of phosphorus compound **848** followed the procedure described for **838** in Scheme X10.

Scheme X12



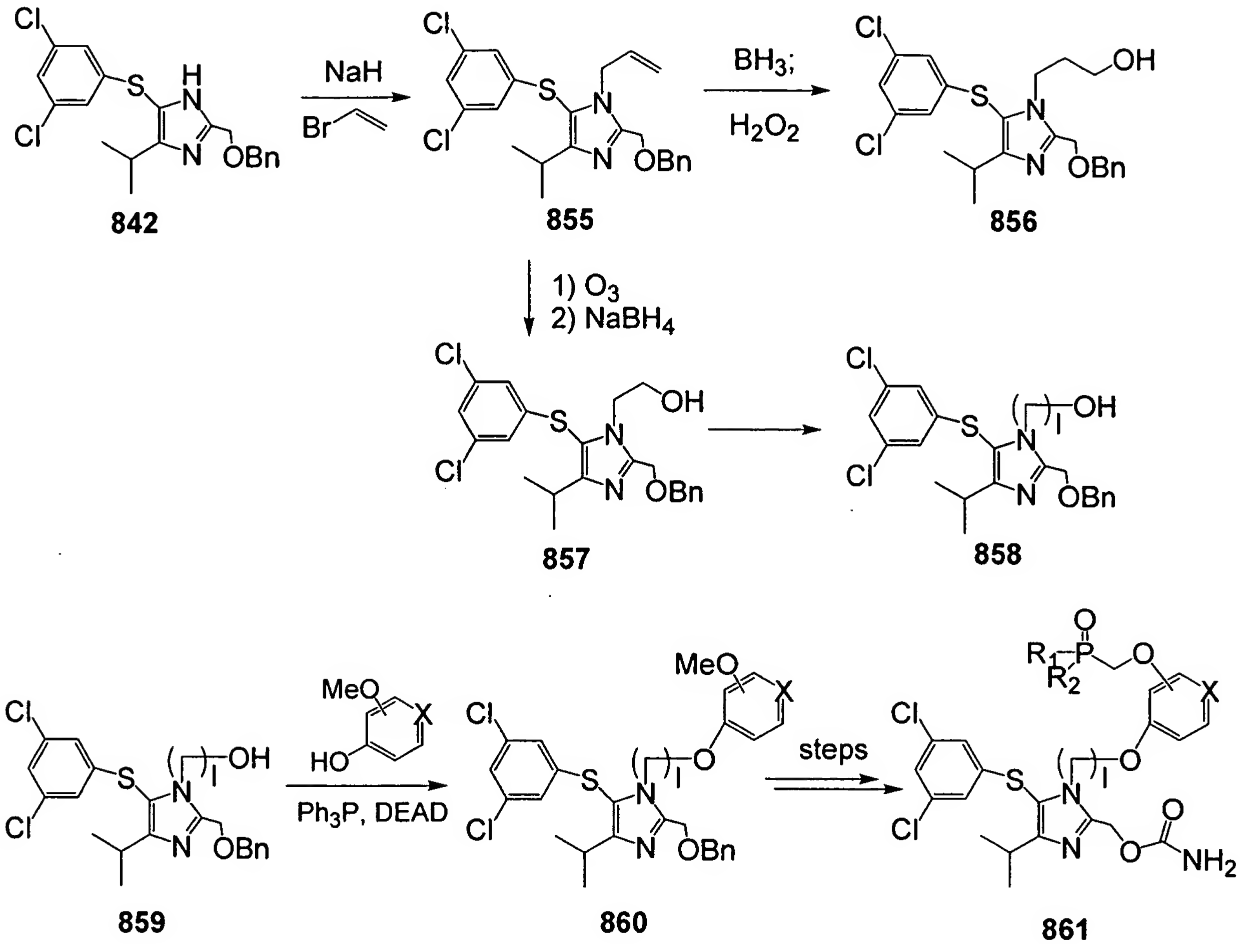
Phosphorus compound **854** was prepared as shown in Scheme X13. Imidazole **849** (prepared according to US Patent Nos. 5910506 and 6057448) was converted to **850** by reacting with chloride in the presence of base. Benzyl and methyl groups were removed by treating ether **850** with strong protonic or Lewis acid to furnish phenol **851**. Treatment of phenol **851** with base followed by triflate **841** gave phosphonate **852**. Following similar procedures described in Scheme X12 transforming alcohol **846** to phosphorus compound **848**, alcohol **852** was converted to phosphorus compound **854**.

Scheme X13



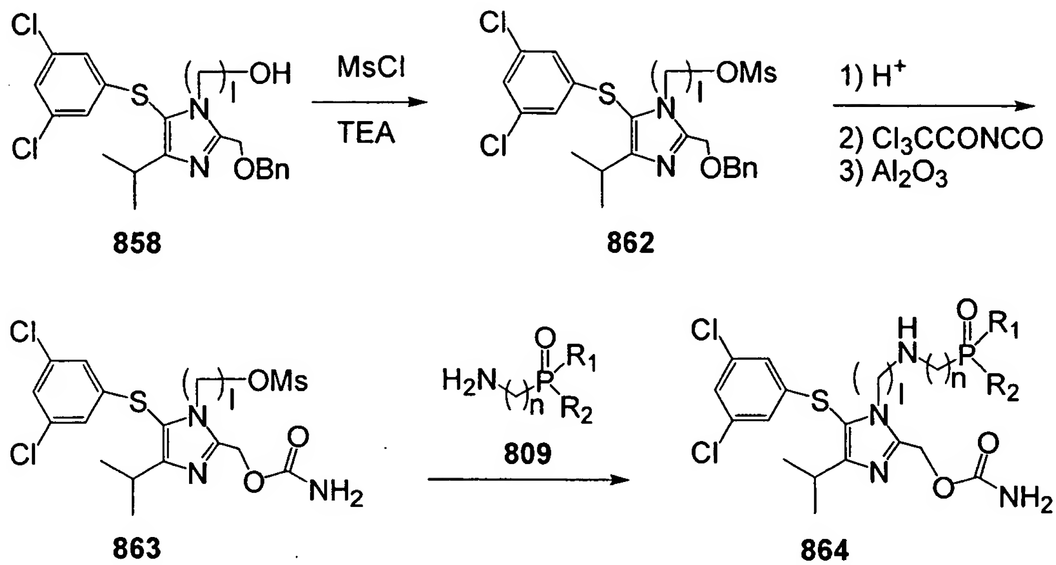
Preparation of phosphorus compound **861** is shown in Scheme X14. Imidazole **855** was synthesized by treating compound **842** with NaH followed by allyl bromide. Hydroboration followed by oxidative work up gave alcohol **856**. Ozonolysis followed by reduction of the resulting aldehyde afforded alcohol **857**. Alcohol **858**, which has variation of length, was obtained by following the same transformation of alcohol **806** to **807** as exhibited in Scheme X7. Mitsunobu reaction of alcohol **859** with substituted phenols gave imidazole **860**. Phenol ether **860** was converted to phosphonate **861** by following same procedure of transforming compound **850** to **854** as described in Scheme X13.

Scheme X14



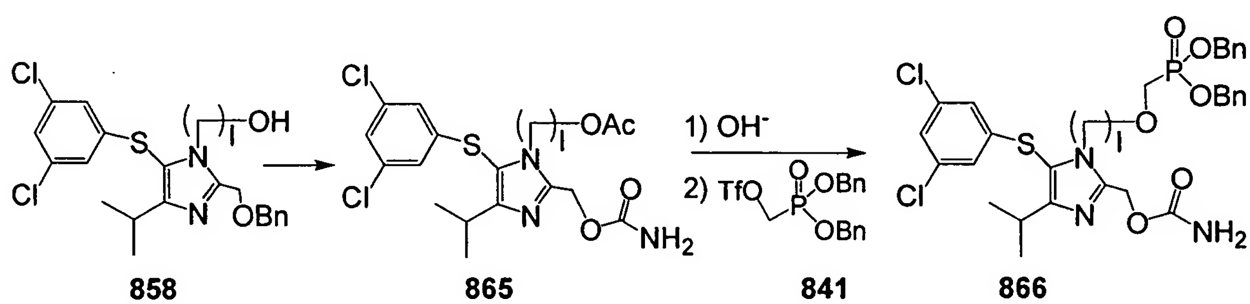
In Scheme X15, preparation of phosphorus compounds **864** is shown. Alcohol **858** was converted to mesylate **862** by reacting with MsCl. Removal of benzyl group, followed by conversion of the resultant alcohol to the corresponding carbamate (described in previous Schemes) furnished compound **863**. Substitution of mesylate with amine **809** generated phosphorus compound **864**.

Scheme X15



Synthesis of phosphorus compound **866** is described in Scheme X16. Protection of alcohol **858** to its acetate **865**, followed by the conversion of the benzyl, —OBn group to the corresponding carbamate as described for transforming compound **862** to **863** in Scheme X15, gave compound **865**. Hydrolysis of acetate, and treatment of the resultant alcohol with triflate **841** in the presence of base afforded phosphonate **866**.

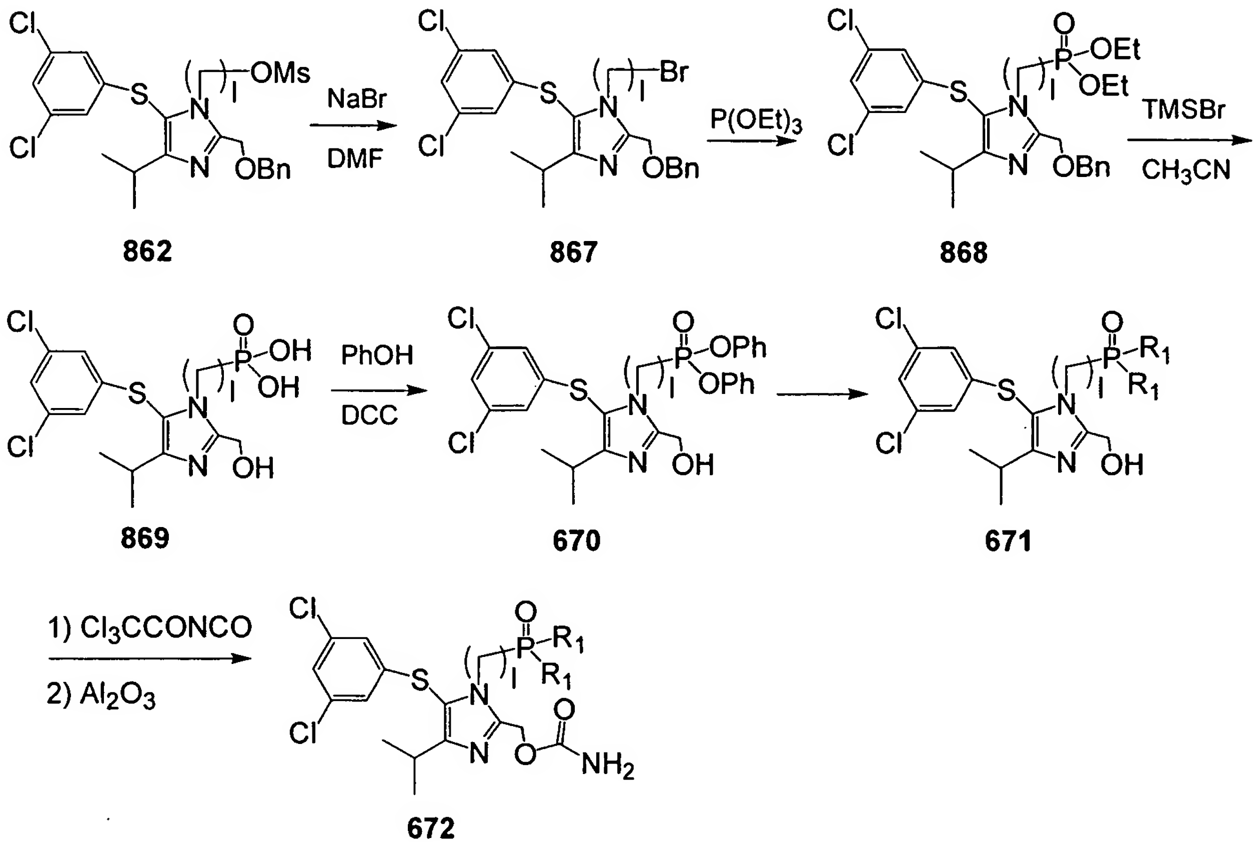
Scheme X16



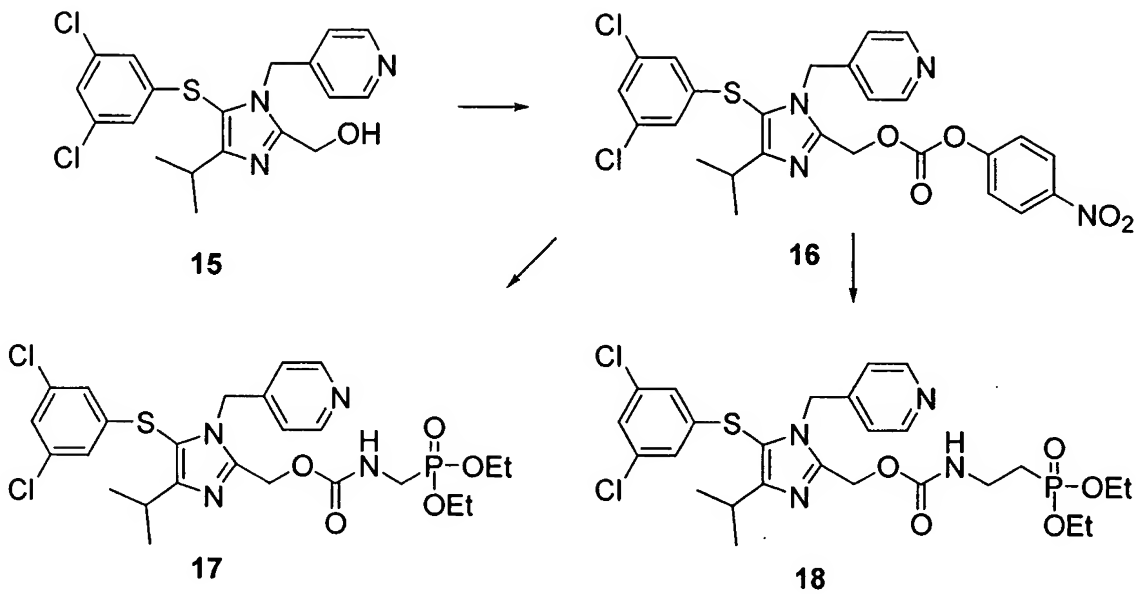
Scheme X17 describes synthesis of phosphorus compound **672**. Mesylate **862** was transformed to bromide **867** by reacting with NaBr. Arbusov reaction gave phosphonate **868**. Both benzyl and ethyl groups were cleaved when treated with TMSBr to yield compound **869**. Coupling of phosphonic acid **869** with PhOH provided bisphenyl phosphonate **670**. Compound **670** was converted to various phosphorus compounds **671** according to the procedures described

in Schemes X1, X2 and X3. Phosphorus compound **672** was obtained by repeating the procedures shown before.

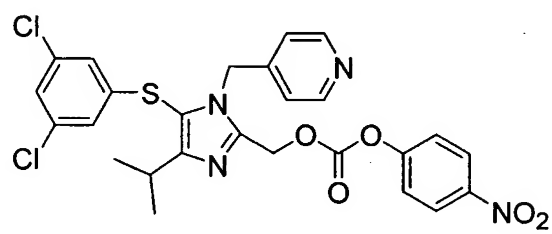
Scheme X17



Scheme X18



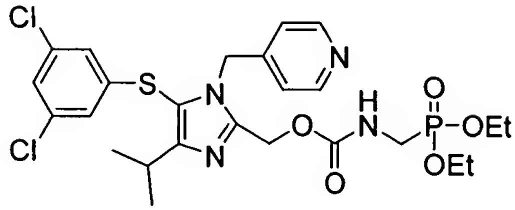
Example X2



16

To a solution of alcohol **15** (42 mg, 0.10 mmol) in CH_2Cl_2 (5 mL) was added triethylamine (24 μL, 0.17 mmol) and bis(4-nitrophenyl) carbonate (46 mg, 0.15 mmol). See Scheme X18. After the reaction mixture was stirred for 4 h at room temperature, the mixture was partitioned between CH_2Cl_2 and water. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 60-70% EtOAc/hexane) to give carbonic acid 5-(3,5-dichloro-phenylsulfanyl)-4-isopropyl-1-pyridin-4-ylmethyl-1H-imidazol-2-ylmethyl ester 4-nitro-phenyl ester **16** (47 mg, 82%) as a colorless oil.

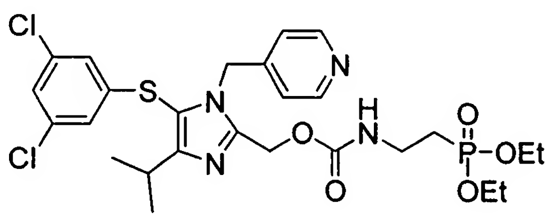
Example X3



17

To a solution of carbonate **16** (14 mg, 0.024 mmol) in CH_3CN (2 mL) was added diethyl(aminomethyl)phosphonate (10 mg, 0.037 mmol) and diisopropylethylamine (8 μL, 0.048 mmol). See Scheme X18. After the reaction mixture was stirred for 16 h at room temperature, the mixture was concentrated under reduced pressure. The residue was purified by preparative thin layer chromatography (eluting 5% $MeOH/CH_2Cl_2$) to give {[5-(3,5-dichloro-phenylsulfanyl)-4-isopropyl-1-pyridin-4-ylmethyl-1H-imidazol-2-ylmethoxycarbonylamino]-methyl}-phosphonic acid diethyl ester **17** (13 mg, 90%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, 2H), 7.04 (t, 1H), 6.78 (d, 2H), 6.68 (d, 2H), 5.25 (s, 2H), 5.19 (s, 2H), 4.98 (bt, 1H), 4.11 (dq, 4H), 3.49 (ABq, 2H), 3.17 (dq, 1H), 1.30 (m, 12H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 21.9.

Example X4

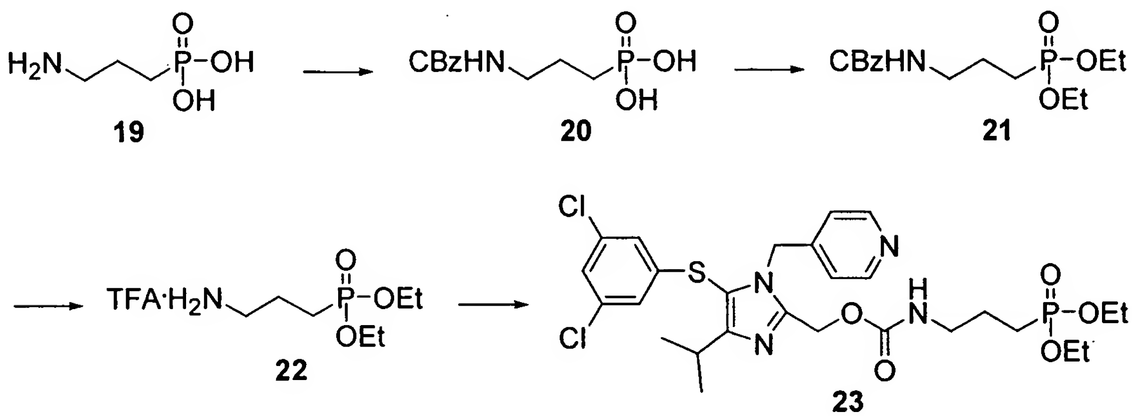


18

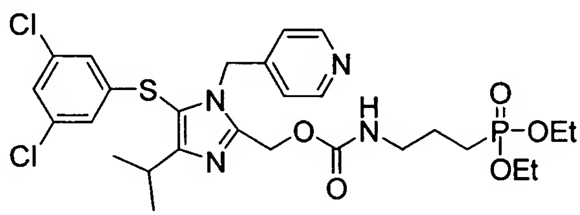
To a solution of carbonate **16** (82 mg, 0.143 mmol) in CH_3CN (5 mL) was added diethyl(aminoethyl)phosphonate (58 mg, 0.214 mmol) and diisopropylethylamine (0.05 mL, 0.286 mmol). See Scheme X20. After the reaction mixture was stirred for 16 h at room temperature, the mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel (eluting 5-7.5% $MeOH/CH_2Cl_2$) to give {2-[5-(3,5-Dichloro-phenylsulfanyl)-4-isopropyl-1-pyridin-4-ylmethyl-1H-imidazol-2-ylmethoxycarbonylamino]-ethyl}-phosphonic acid diethyl ester **18** (79 mg, 90%) as a pale yellow oil. ^{1}H NMR (300 MHz,

$CDCl_3$) δ 8.43 (d, 2H), 7.02 (s, 1H), 6.77 (d, 2H), 6.67 (s, 2H), 5.32 (t, 1H), 5.24 (s, 2H), 5.16 (s, 2H), 4.08 (m, 4H), 3.35 (m, 2H), 3.15 (m, 1H), 1.86 (m, 2H), 1.30 (m, 6H), 1.29 (s, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 31.5.

Scheme X19



Example X5



23

To a solution of 3-aminopropylphosphonic acid **19** (500 g, 3.59 mmol) in 2N NaOH (3.6 mL, 7.19 mmol) was added benzyl chloroformate (0.62 mL, 4.31 mmol) according to Scheme X19. After the reaction mixture was stirred for 16 hours at room temperature, the mixture was partitioned between Et_2O and water. The aqueous phase was acidified with 6N HCl until pH = 2. The resulting colorless solid was dissolved in MeOH (75 mL) and treated with Dowex 50WX8-200 (2.5 g). After the mixture was stirred for 30 minutes, it was filtered and evaporated under reduced pressure to give carbamate **20** (880 mg, 90%) as a colorless solid.

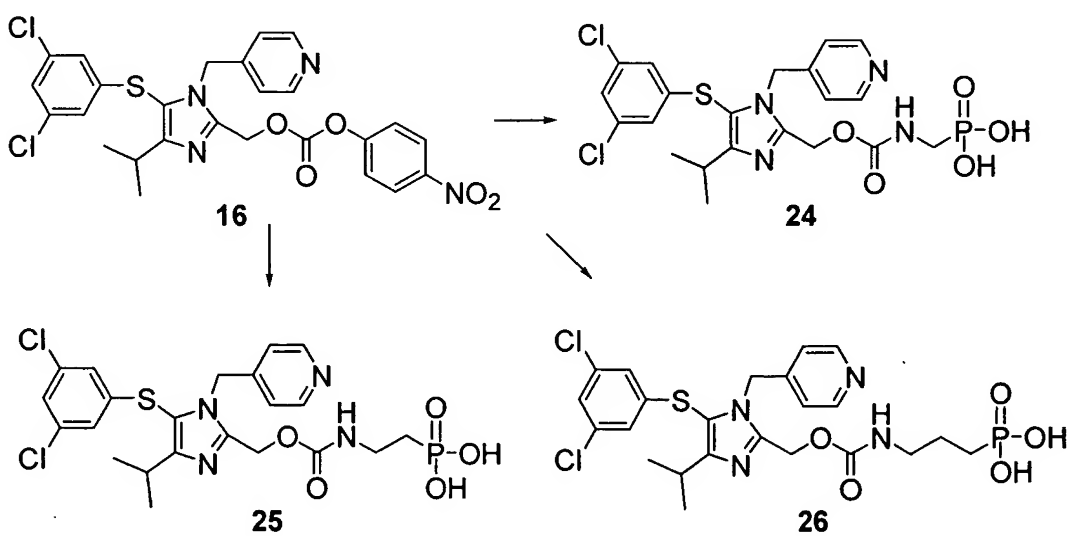
To a solution of carbamate **20** (246 mg, 0.90 mmol) in benzene (5 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene phenol (0.27 mL, 1.8 mmol) and iodoethane (0.22 mL, 2.7 mmol). After the reaction mixture was warmed to 60°C and stirred for 16 h, the mixture was concentrated under reduced pressure and partitioned between EtOAc and sat. NH_4Cl. The crude

product was chromatographed on silica gel (eluting 3-4% $MeOH/CH_2Cl_2$) to give phosphonate **21** (56 mg, 19%) as a colorless oil.

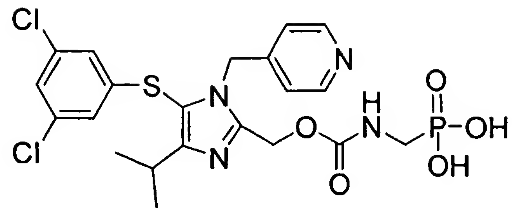
To a solution of phosphonate **21** (56 mg, 0.17 mmol) in EtOH (3 mL) was added TFA (13 μL, 0.17 mmol) and 10% Pd/C (11 mg). After the reaction mixture was stirred under H_2 atmosphere (balloon) for 1 h, the mixture was filtered through Celite. The filtrate was evaporated under reduced pressure to give amine **22** (52 mg, 99%) as a colorless oil.

To a solution of carbonate **16** (15 mg, 0.026 mmol) in CH_3CN (2 mL) was added diethyl(aminopropyl)phosphonate (16 mg, 0.052 mmol) and diisopropylethylamine (11 μL, 0.065 mmol). After the reaction mixture was stirred for 16 h at room temperature, the mixture was concentrated under reduced pressure. The residue was purified by preparative thin layer chromatography (eluting 5% $MeOH/CH_2Cl_2$) to give {3-[5-(3,5-dichloro-phenylsulfanyl)-4-isopropyl-1-pyridin-4-ylmethyl-1H-imidazol-2-ylmethoxycarbonylamino]-propyl}-phosphonic acid diethyl ester **23** (13 mg, 79%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, 2H), 7.04 (t, 1H), 6.80 (d, 2H), 6.68 (d, 2H), 5.26 (s, 2H), 5.18 (s, 2H), 5.08 (bt, 1H), 4.08 (m, 4H), 3.15 (m, 3H), 1.72 (m, 4H), 1.31 (m, 12H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 31.5.

Scheme X20



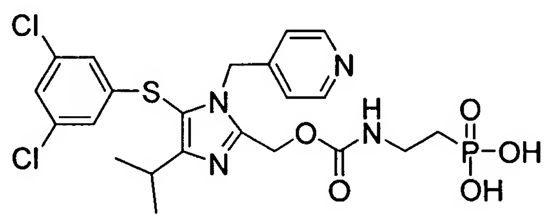
Example X6



24

To a solution of aminomethylphosphonic acid (8 mg, 0.073 mmol) in water (1 mL) was added 1N NaOH (0.15 mL, 0.15 mmol) and carbonate **16** (21 mg, 0.037 mmol) in dioxane (1 mL). See Scheme X20. After the reaction mixture was stirred for 6 h at room temperature, the mixture was concentrated under reduced pressure. The residue was purified by HPLC on C18 reverse phase chromatography (eluting 30% CH_3CN/water) to give a mixture of phosphonic acid **24** and alcohol **15**. The mixture was further purified by preparative thin layer chromatography (eluting 7.5% MeOH/CH_2Cl_2) to give {[5-(3,5-dichloro-phenylsulfanyl)-4-isopropyl-1-pyridin-4-ylmethyl-1H-imidazol-2-ylmethoxycarbonyl amino]-methyl}-phosphonic acid **24** (8 mg, 40%) as a colorless solid. ^{1}H NMR (300 MHz, CD_3OD) δ 8.33 (bs, 2H), 7.10 (t, 1H), 7.04 (bs, (2H), 6.72 (d, 2H), 5.44 (s, 2H), 5.25 (s, 2H), 3.24 (m, 2H), 3.17 (m, 1H), 1.28 (d, 6H).

Example X7

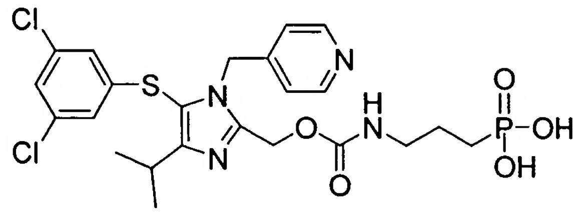


25

To a solution of 2-aminoethylphosphonic acid (12 mg, 0.098 mmol) in water (1 mL) was added 1N NaOH (0.2 mL, 0.20 mmol) and carbonate **16** (28 mg, 0.049 mmol) in dioxane (1 mL). See Scheme X20. After the reaction mixture was stirred for 6 h at room temperature, the mixture was concentrated under reduced pressure. The residue was purified by HPLC on C18 reverse phase chromatography (eluting 30% CH_3CN/water) to give a mixture of phosphonic acid **25** and alcohol **15**. The mixture was further purified by preparative thin layer chromatography (eluting 7.5% MeOH/CH_2Cl_2) to give {2-[5-(3,5-dichloro-phenylsulfanyl)-4-isopropyl-1-pyridin-4-ylmethyl-1H-imidazol-2-ylmethoxycarbonylamino]-ethyl}-phosphonic acid **25** (13 mg, 47%) as

a colorless solid. ^1H NMR (300 MHz, CD_3OD) δ 8.32 (d, 2H), 7.11 (s, 1H), 7.02 (d, 2H), 6.72 (s, 2H), 5.42 (s, 2H), 5.23 (s, 2H), 3.30 (m, 2H), 3.17 (m, 1H), 1.71 (m, 2H), 1.28 (d, 6H). ^{31}P NMR (300 MHz, CD_3OD) δ 20.1.

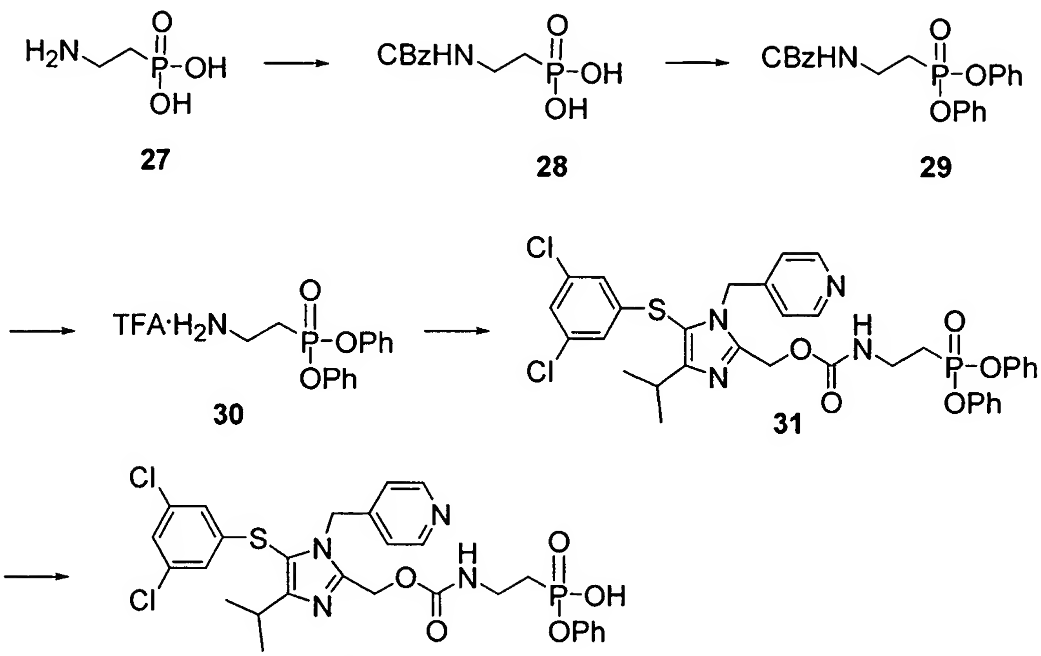
Example X8



26

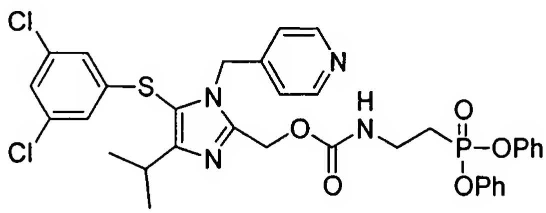
To a solution of 3-aminopropylphosphonic acid (12 mg, 0.084 mmol) in water (1 mL) was added 1N NaOH (0.17 mL, 0.17 mmol) and carbonate **16** (24 mg, 0.042 mmol) in dioxane (1 mL). See Scheme X20. After the reaction mixture was stirred for 6 h at room temperature, the mixture was concentrated under reduced pressure. The residue was purified by HPLC on C18 reverse phase chromatography (eluting 30% CH_3CN/water) to give a mixture of phosphonic acid **26** and alcohol **15**. The mixture was further purified by preparative thin layer chromatography (eluting 7.5% MeOH/CH_2Cl_2) to give {3-[5-(3,5-dichloro-phenylsulfanyl)-4-isopropyl-1-pyridin-4-ylmethyl-1H-imidazol-2-ylmethoxycarbonylamino]-propyl}-phosphonic acid **26** (11 mg, 46%) as a colorless solid. ^1H NMR (300 MHz, CD_3OD) δ 8.34 (bs, 2H), 7.11 (s, 1H), 7.02 (bs, 2H), 6.73 (d, 2H), 5.43 (s, 2H), 5.23 (s, 2H), 3.32 (m, 1H), 3.06 (bs, 2H), 1.69 (bs, 2H), 1.50 (bs, 2H), 1.28 (d, 6H).

Scheme X21



27 28 29 30 31 32

Example X9



31

To a solution of 2-aminoethylphosphonic acid (1.26 g, 10.1 mmol) in 2N NaOH (10.1 mL, 20.2 mmol) was added benzyl chloroformate (1.7 mL, 12.1 mmol). See Scheme X21. After the reaction mixture was stirred for 2 d at room temperature, the mixture was partitioned between Et_2O and water. The aqueous phase was acidified with 6N HCl until pH = 2. The resulting colorless solid was dissolved in MeOH (75 mL) and treated with Dowex 50WX8-200 (7 g). After the mixture was stirred for 30 minutes, it was filtered and evaporated under reduced pressure to give carbamate **28** (2.37 g, 91%) as a colorless solid.

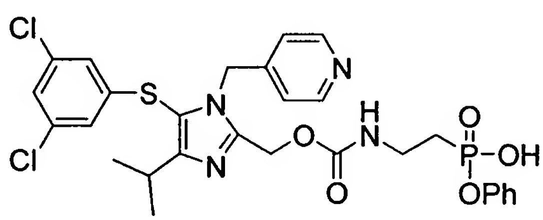
To a solution of carbamate **28** (2.35 g, 9.1 mmol) in pyridine (40 mL) was added phenol (8.53 g, 90.6 mmol) and 1,3-dicyclohexylcarbodiimide (7.47 g, 36.2 mmol). After the reaction mixture was warmed to 70°C and stirred for 5 h, the mixture was diluted with CH_3CN and

filtered. The filtrate was concentrated under reduced pressure and diluted with EtOAc. The organic phase was washed with sat. NH_4Cl, sat. $NaHCO_3$, and brine, then dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel twice (eluting 40-60% EtOAc/hexane) to give phosphonate **29** (2.13 g, 57%) as a colorless solid.

To a solution of phosphonate **29** (262 mg, 0.637 mmol) in isopropanol (iPrOH) (5 mL) was added TFA (0.05 mL, 0.637 mmol) and 10% Pd/C (26 mg). After the reaction mixture was stirred under H_2 atmosphere (balloon) for 1 h, the mixture was filtered through Celite. The filtrate was evaporated under reduced pressure to give amine **30** (249 mg, 100%) as a colorless oil.

To a solution of carbonate **16** (40 mg, 0.070 mmol) and amine **30** (82 mg, 0.21 mmol) in CH_3CN (5 mL) was added diisopropylethylamine (0.05 mL, 0.28 mmol). After the reaction mixture was stirred for 2 h at room temperature, the mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel (eluting 3-4% MeOH/CH_2Cl_2) to give {2-[5-(3,5-dichloro-phenylsulfanyl)-4-isopropyl-1-pyridin-4-ylmethyl-1H-imidazol-2-ylmethoxycarbonylamino]-ethyl}-phosphonic acid diphenyl ester **31** (36 mg, 72%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, 2H), 7.22 (m, 4H), 7.14 (m, 2H), 7.10 (m, 2H), 6.99 (t, 1H), 6.72 (d, 2H), 6.62 (d, 2H), 5.30 (bt, 1H), 5.18 (s, 2H), 5.13 (s, 2H), 3.50 (m, 2H), 3.12 (m, 1H), 2.21 (m, 2H), 1.26 (d, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 22.4.

<u>Example X10</u>

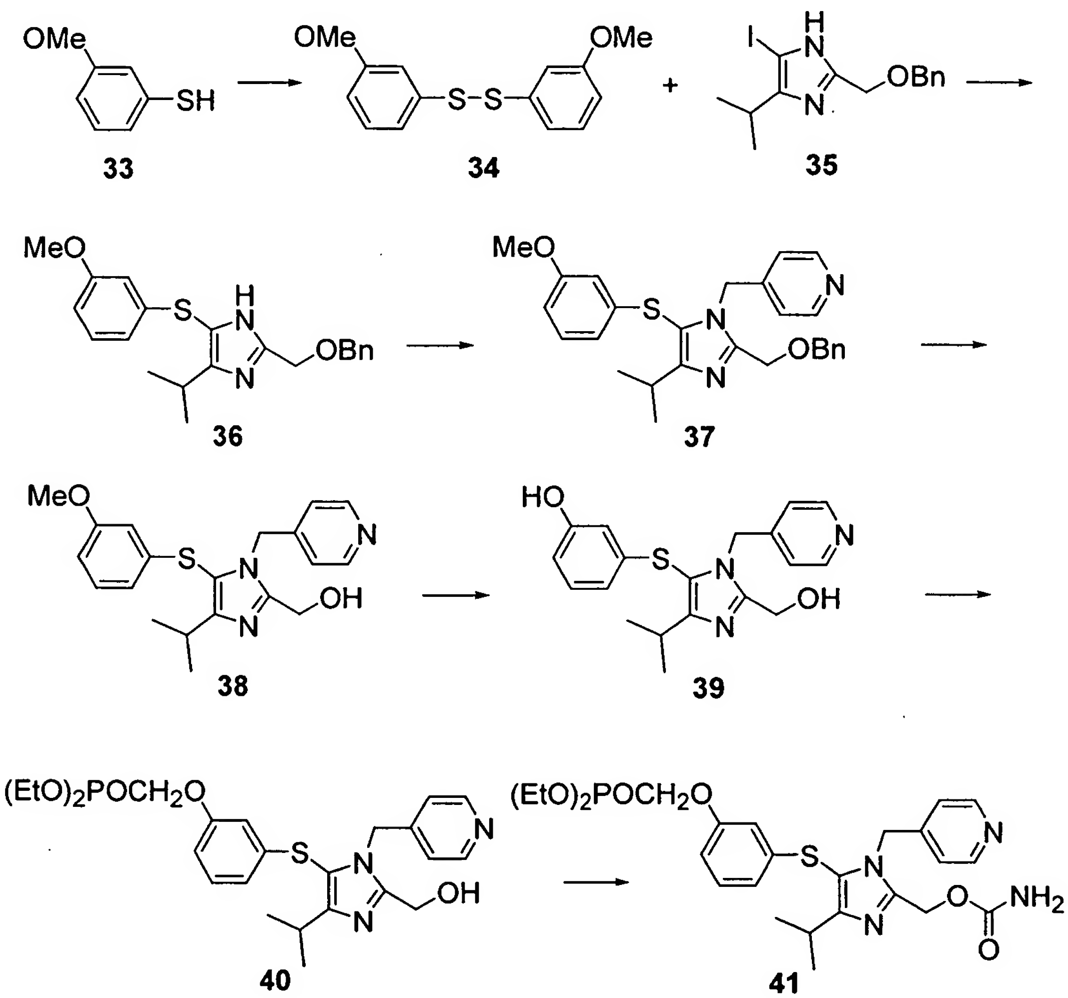


32

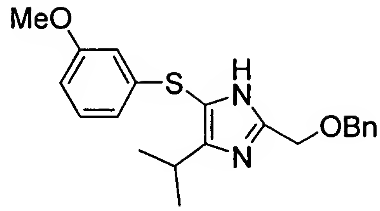
To a solution of phosphonate **31** (11 mg, 0.015 mmol) in CH_3CN (0.5 mL) was added 1N LiOH (46 μL, 0.046 mmol) at 0°C. See Scheme X21. After the reaction mixture was stirred for 2 h at 0°C, Dowex 50WX8-200 (26 mg) was added and stirring was continued for an additional 30 min. The reaction mixture was filtered, rinsed with CH_3CN, and concentrated under reduced

pressure to give {2-[5-(3,5-dichloro-phenylsulfanyl)-4-isopropyl-1-pyridin-4-ylmethyl-1H-imidazol-2-ylmethoxycarbonylamino]-ethyl}-phosphonic acid monophenyl ester **32** (10 mg, 100%) as a colorless oil. ^{1}H NMR (300 MHz, CD_3OD) δ 8.52 (d, 2H), 7.28 (m, 6H), 6.79 (m, 4H), 5.60 (s, 2H), 5.29 (s, 2H), 3.29 (m, 3H), 1.83 (m, 2H), 1.31 (d, 6H). ^{31}P NMR (300 MHz, CD_3OD) δ 20.2.

Scheme X22



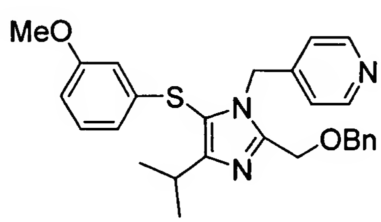
Example X11



36

To a solution of 3-methoxybenzenethiol (0.88 mL, 7.13 mmol) in CH_3CN (15 mL) was added sodium iodide (214 mg, 1.43 mmol) and ferric chloride (232 mg, 1.43 mmol). See Scheme X22. After the reaction mixture was warmed to 60°C and stirred for 3 d, the mixture was concentrated under reduced pressure and partitioned between CH_2Cl_2 and water. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 5-6% EtOAc/hexane) to give disulfide **34** (851 mg, 86%) as a yellow oil. To a solution of disulfide **34** (850 mg, 3.05 mmol) in DMSO (10 mL) was added iodide **35**, also denoted previously as compound **842**, (1.21 g, 3.39 mmol) and lithium hydride (32 mg, 4.07 mmol). After the reaction mixture was warmed to 60°C and stirred for 16 h, the mixture was partitioned between EtOAc and water. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 30-50% EtOAc/hexane) to give 2-benzyloxymethyl-4-isopropyl-5-(3-methoxy-phenylsulfanyl)-1H-imidazole **36** (247 mg, 22%) as a yellow oil.

Example X12

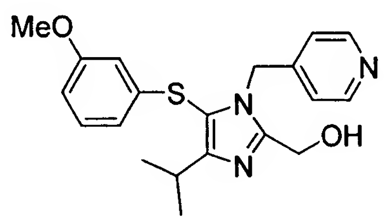


37

To a solution of sulfide **36** (247 mg, 0.67 mmol) in THF (10 mL) was added 4-picolylchloride (220 mg, 1.34 mmol), powder NaOH (59 mg, 1.47 mmol), lithium iodide (44 mg,

0.33 mmol), and tetrabutylammonium bromide (22 mg, 0.067 mmol). See Scheme X22. After the reaction mixture was stirred for 2 d at room temperature, the mixture was partitioned between EtOAc and sat. NH_4Cl. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 60-100% EtOAc/hexane) to give 4-[2-benzyloxymethyl-4-isopropyl-5-(3-methoxy-phenylsulfanyl)-imidazol-1-ylmethyl]-pyridine **37** (201 mg, 65%) as a yellow oil.

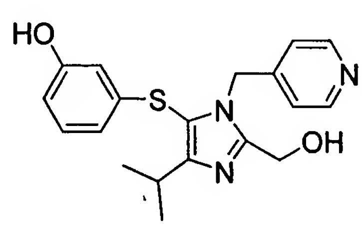
Example X13



38

To a solution of amine **37** (101 mg, 0.220 mmol) in EtOH (5 mL) was added conc. HCl (5 mL). See Scheme X22. After the reaction mixture was warmed to 80°C and stirred for 16 h, the mixture was concentrated under reduced pressure and partitioned between EtOAc and sat. $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 5-7% $MeOH/CH_2Cl_2$) to give [4-isopropyl-5-(3-methoxy-phenylsulfanyl)-1-pyridin-4-ylmethyl-1H-imidazol-2-yl]-methanol **38** (71 mg, 87%) as a pale yellow oil.

Example X14

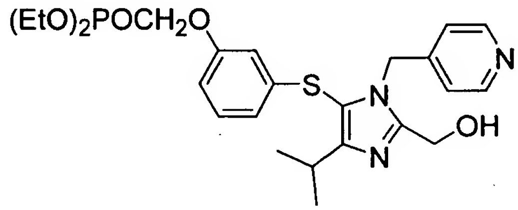


39

To a solution of alcohol **38** (56 mg, 0.15 mmol) in CH_2Cl_2 (2 mL) was added 1M BBr_3 in CH_2Cl_2 at 0°C. See Scheme X22. After the reaction mixture was stirred for 1 h at 0°C, the

mixture was partitioned between CH_2Cl_2 and sat. $NaHCO_3$. The aqueous phase was neutralized with solid $NaHCO_3$ and extracted with CH_2Cl_2 and EtOAc. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 5-10% MeOH/CH_2Cl_2) to give 3-(2-hydroxymethyl-5-isopropyl-3-pyridin-4-ylmethyl-3H-imidazol-4-ylsulfanyl)-phenol **39** (43 mg, 81%) as a colorless solid.

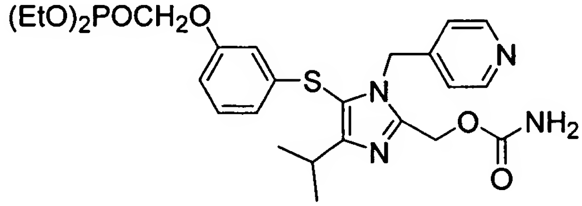
Example X15



40

To a solution of phenol **39** (25 mg, 0.070 mmol) and triflate (33 mg, 0.11 mmol) in THF (2 mL) and CH_3CN (2 mL) was added Cs_2CO_3 (46 mg, 0.14 mmol). See Scheme X22. After the reaction mixture was stirred for 1 h at room temperature, the mixture was partitioned between EtOAc and water. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by preparative thin layer chromatography (eluting 10% MeOH/CH_2Cl_2) to give [3-(2-Hydroxymethyl-5-isopropyl-3-pyridin-4-ylmethyl-3H-imidazol-4-ylsulfanyl)-phenoxymethyl]-phosphonic acid diethyl ester **40** (10 mg, 28%) as a colorless oil.

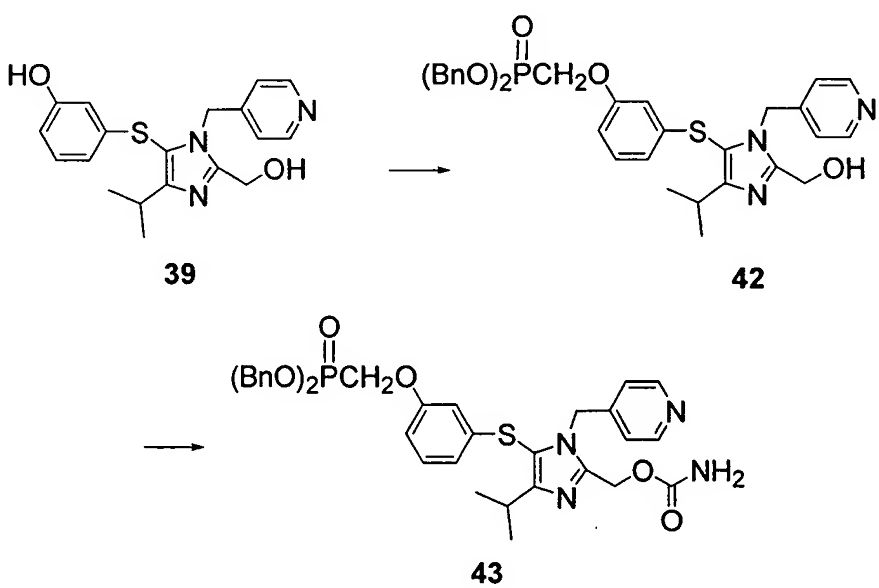
Example X16



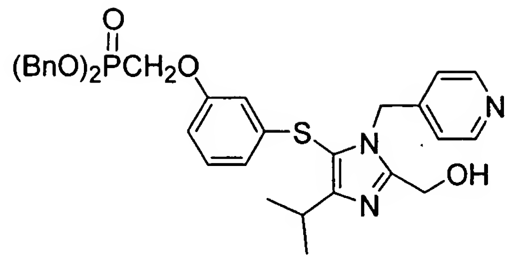
41

To a solution of diethylphosphonate **40** (10 mg, 0.020 mmol) in THF (2 mL) was added trichloroacetyl isocyanate (7 μL, 0.059 mmol). See Scheme X22. After the reaction mixture was stirred for 30 min at room temperature, the mixture was evaporated under reduced pressure. To a solution of the concentrated residue in MeOH (2 mL) was added 1M K_2CO_3 (0.2 mL, 0.20 mmol) at 0°C. After the reaction mixture was warmed to room temperature and stirred for 3 h, the mixture was partitioned between EtOAc and sat. NH_4Cl. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by preparative thin layer chromatography (eluting 10% MeOH/CH_2Cl_2) to give [3-(2-hydroxymethyl-5-isopropyl-3-pyridin-4-ylmethyl-3H-imidazol-4-ylsulfanyl)-phenoxymethyl]-phosphonic acid diethyl ester **41** (10 mg, 91%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (d, 2H), 7.16 (m, 1H), 6.85 (m, 1H), 6.75 (m, 1H), 6.73 (m, 1H), 6.17 (s, 1H), 5.31 (s, 2H), 5.02 (s, 2H), 4.23 (m, 4H), 4.16 (d, 2H), 3.23 (m, 1H), 1.37 (t, 6H), 1.29 (d, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 19.6.

Scheme X23



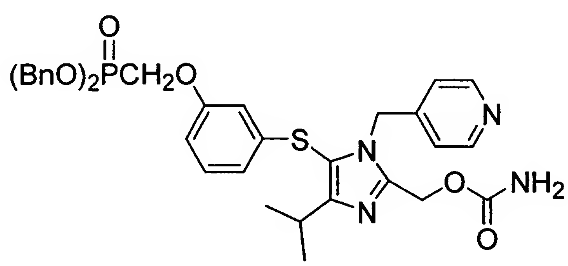
Example X17



42

To a solution of phenol **39** (20 mg, 0.056 mmol) in THF (1 mL) and CH_3CN (1 mL) was added sodium hydride (60%, 5 mg, 0.112 mmol) at 0°C. See Scheme X23. After the reaction mixture was stirred for 30 min at 0°C, dibenzylphosphonyl methyltriflate (21 mg, 0.050 mmol) in THF (1 mL) was added. After the reaction mixture was stirred for 1 h at 0°C, the mixture was evaporated under reduced pressure and partitioned between EtOAc and sat. NH_4Cl. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by preparative thin layer chromatography (eluting 10% $MeOH/CH_2Cl_2$) to give dibenzylphosphonate **42** (5 mg, 16%) as a pale yellow oil.

Example X18



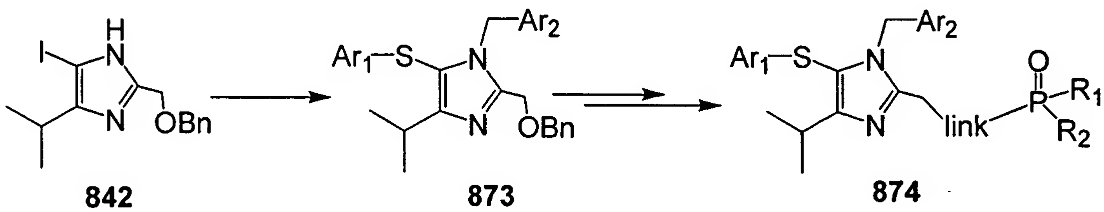
43

To a solution of dibenzylphosphonate **42** (5 mg, 0.0079 mmol) in CH_2Cl_2 (1 mL) was added trichloroacetyl isocyanate (5 μL, 0.049 mmol). See Scheme X23. After the reaction mixture was stirred for 15 min at room temperature, the mixture was transferred on to a 2-inch column of neutral Al_2O_3. After the reaction mixture was soaked for 30 min, the mixture was rinsed off the column with 10% $MeOH/CH_2Cl_2$ and evaporated under reduced pressure. The crude product was purified by preparative thin layer chromatography (eluting 10% $MeOH/CH_2Cl_2$) to give carbamate **43** (3 mg, 56%) as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, 2H), 7.35 (m, 10H), 7.12 (t, 1H), 6.88 (m, 2H), 6.70 (d, 1H), 6.66 (dd, 1H),

6.10 (t, 1H), 5.29 (s, 2H), 5.13 (dd, 6H), 5.05 (s, 2H), 4.14 (d, 2H), 3.24 (m, 1H), 1.30 (d, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 20.3.

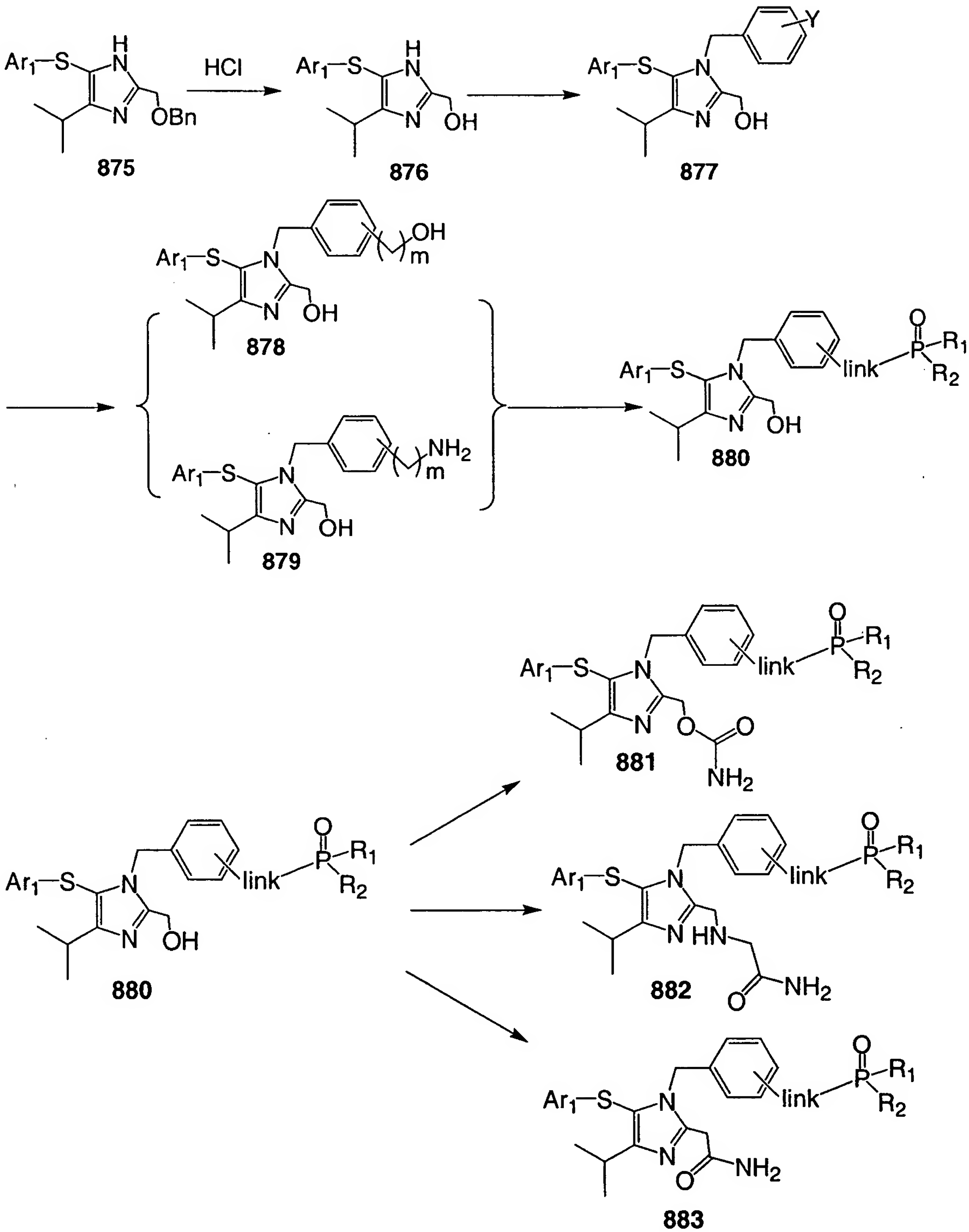
Preparation of phosphorus compound **874** was displayed in Scheme X24. Starting with imidazole **842**, Ar1 and Ar2 were introduced following the procedure described in US Patent No. 5326780. Benzyl group was then removed and converted to phosphorus analog **874** using the procedure described previously.

Scheme X24



Scheme X25 describes preparation of compound **880**. Compound **875** was synthesized from compound **842** using the procedures described in US Patent No. 5326780. Treatment of **875** with HCl removed the benzyl group to give alcohol **876**, which was then introduced phenyl group with substitution of Y. Y is a function which can be converted to alcohol, aldehyde or amine, for example $-NO_2$, -COOMe, N_3, and etc. Conversion of Y to the amine or alcohol gave compound **878** and/or **879**, which were then used as attachment site of phosphorus to afford phosphorus compound **880**. Hydroxyl group in compound **880** was then converted to the desired side chain including but not limit to carbamate **881**, urea **882**, substituted amine **883**.

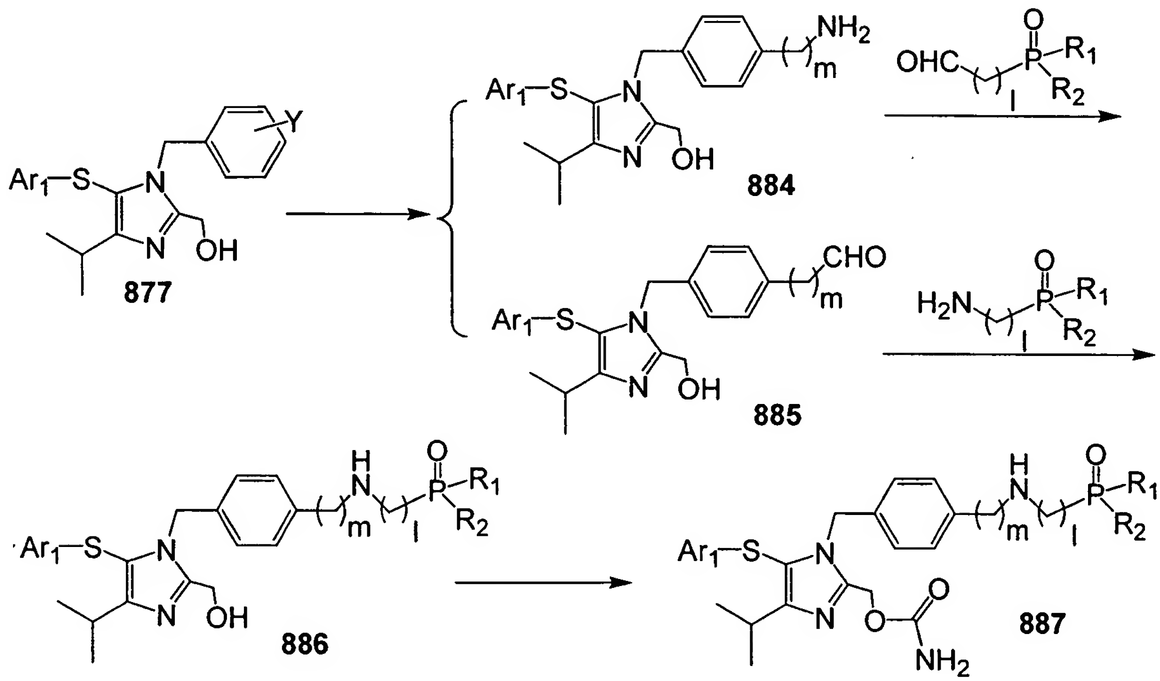
Scheme X25



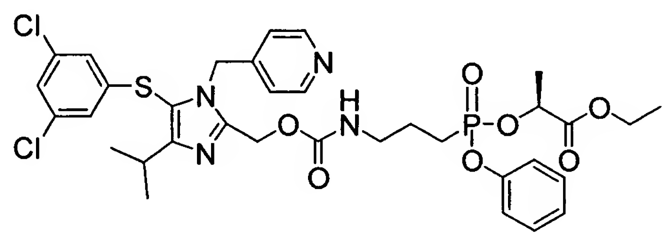
Preparation of phosphorus compound **887** is shown in Scheme X26. Compound **877** was converted to amine **884** and/or aldehyde **885**, which then reacted with aldehyde and/or amine

respectively to provide phosphorus compound **886**. Treatment of compound **886** with $Cl_3CCONCO$ provide the carbamate **887**.

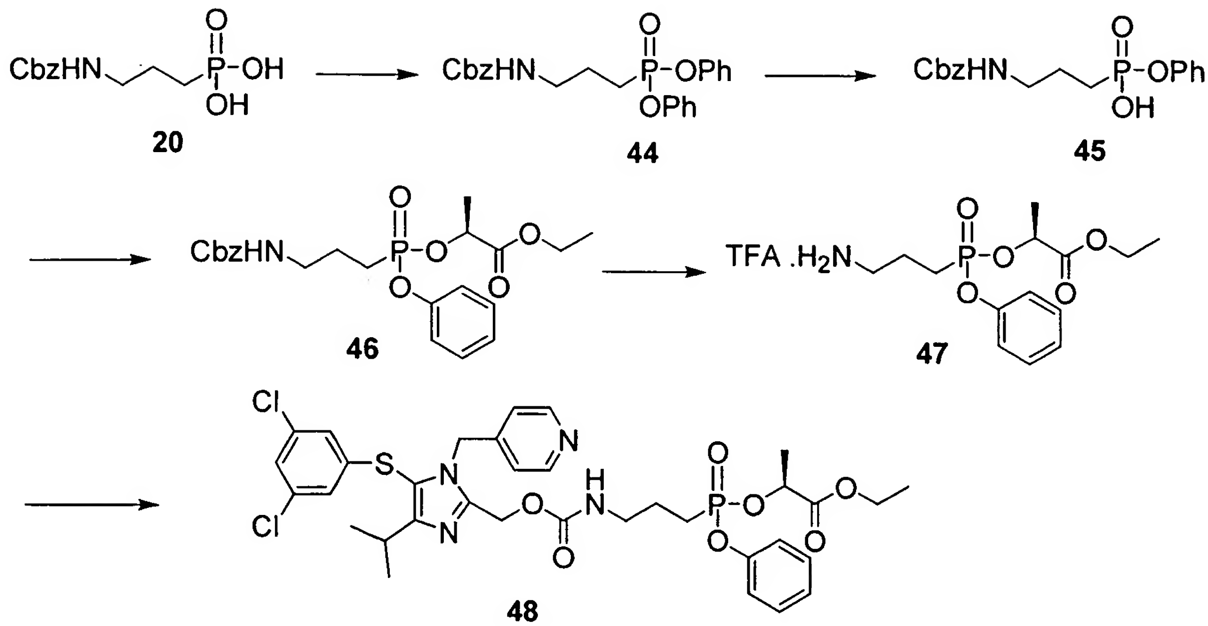
Scheme X26



<u>Example X19</u>

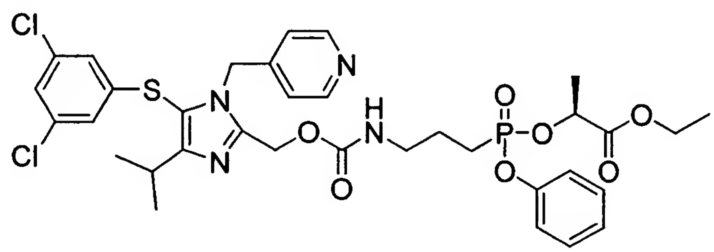


48



Compound **44** was prepared following the sequence of steps described in Example X9, by substituting compound **20** for compound **28**. Purification of the crude product on silica gel eluted with 3-4% MeOH/CH_2Cl_2 provided 37 mg of **48**, the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) (1.3:1 diastereomeric ratio) δ 8.50 (bs, 2H), 7.35 (t, 2H), 7.20 (m, 3H), 7.06 (s, 1H), 6.90 (bs, 2H), 6.70 (s, 2H), 5.26 (bs, 2H), 5.21 (s, 2H), 4.97 (m, 1H), 4.22 (q, 2H), 3.24 (m, 2H), 3.19 (m, 1H), 2.05 (m, 2H), 1.92 (m, 2H), 1.37 (d, 3H), 1.33 (d, 6H), 1.28 (t, 3H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 30.0.

<u>Example X20</u>

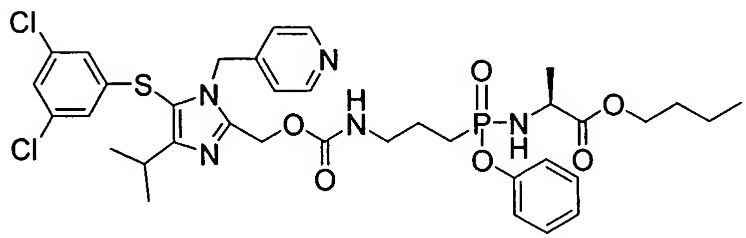


49

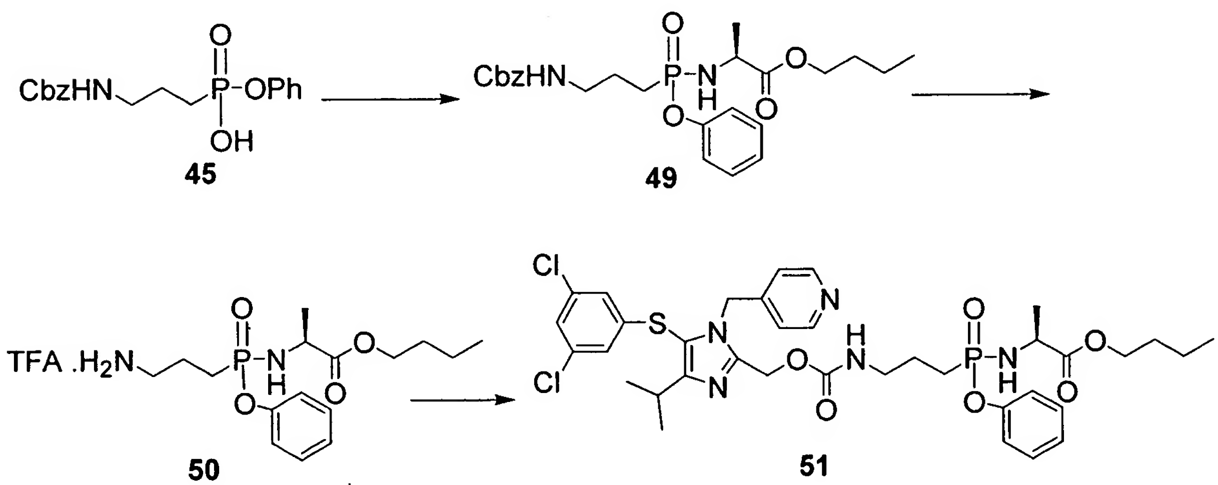
The title compound **49** was prepared following the sequence of steps described in Example X19, except for using scalmeric mixture **46** (around 13:1 ratio). Purification of the crude final product on silica gel eluted with 3-4% MeOH/CH_2Cl_2 provided 40 mg of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (bd, 2H), 7.32 (m, 2H), 7.19 (m, 3H), 7.04 (d,

1H), 6.80 (bs, 2H), 6.68 (m, 2H), 5.27 (d, 2H), 5.19 (d, 2H), 4.96 (m, 1H), 4.15 (m, 2H), 3.18 (m, 3H), 1.93 (m, 4H), 1.55 (d, 1.5H), 1.34 (d, 1.5H), 1.31 (d, 6H), 1.21 (m, 3H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 30.0, 28.3.

<u>Example X21</u>



51

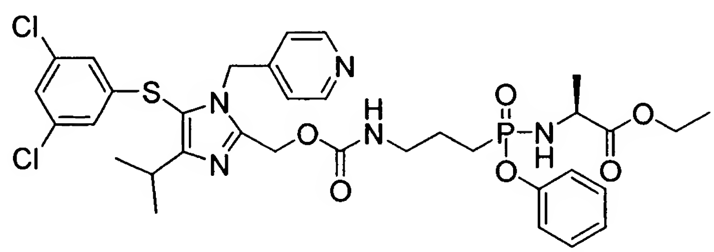


Amidate **49**: A solution of phosphonic acid **45** (66 mg, 0.19 mmol) in CH_3CN (5 mL) was treated with thionyl chloride (42 μL, 0.57 mmol). After the reaction mixture was warmed to 70°C and stirred for 2 h, the mixture was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (5 mL) and cooled to 0°C. Triethylamine (0.11 mL, 0.76 mmol) and L-alanine *n*-butyl ester (104 mg, 0.57 mmol) were added. After stirring for 1 h at 0°C and 1 h at room temperature, the reaction mixture was neutralized with sat. NH_4Cl and extracted with CH_2Cl_2 and EtOAc. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified on silica gel (eluting 60-80% EtOAc/hexane) to give amidate **49** (35 mg, 39%) as a colorless oil.

Amine **50**: A mixture of benzyl carbamate **49** (35 mg, 0.073 mmol), trifluoroacetic acid (8 μL, 0.11 mmol) and 10% Pd/C (7 mg) in isopropyl alcohol (2 mL) was stirred under H_2 atmosphere (balloon) for 1 h. The mixture was then filtered through Celite. The filtrate was evaporated under reduced pressure to give amine **50** (33 mg, 99%) as a colorless oil.

Title compound **51**: A solution of 4-nitrophenylcarbonate **16** (35 mg, 0.061 mmol) in CH_3CN (2 mL) was treated with amine **50** (33 mg, 0.072 mmol) and iPr_2NEt (21 μL, 0.122 mmol). After the reaction mixture was stirred for 1 h at room temperature, the mixture was concentrated under reduced pressure. The residue was purified on silica gel (eluting 4-5% $MeOH/CH_2Cl_2$) to give the title compound **51** (43 mg, 91%) as a pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 8.46 (bs, 2H), 7.31 (m, 2H), 7.20 (d, 2H), 7.14 (m, 1H), 7.05 (s, 1H), 6.81 (bd, 2H), 6.71 (d, 2H), 5.27 (bs, 2H), 5.19 (bs, 2H), 4.07 (m, 2H), 3.98 (m, 1H), 3.63 (m, 1H), 3.18 (m, 3H), 1.83 (m, 2H), 1.80 (m, 2H), 1.58 (m, 2H), 1.35 (m, 2H), 1.32 (d, 6H), 1.30 (d, 1.5H), 1.24 (d, 1.5H), 0.93 (t, 3H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 31.6, 31.3.

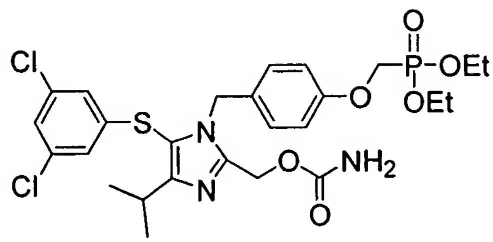
Example X22



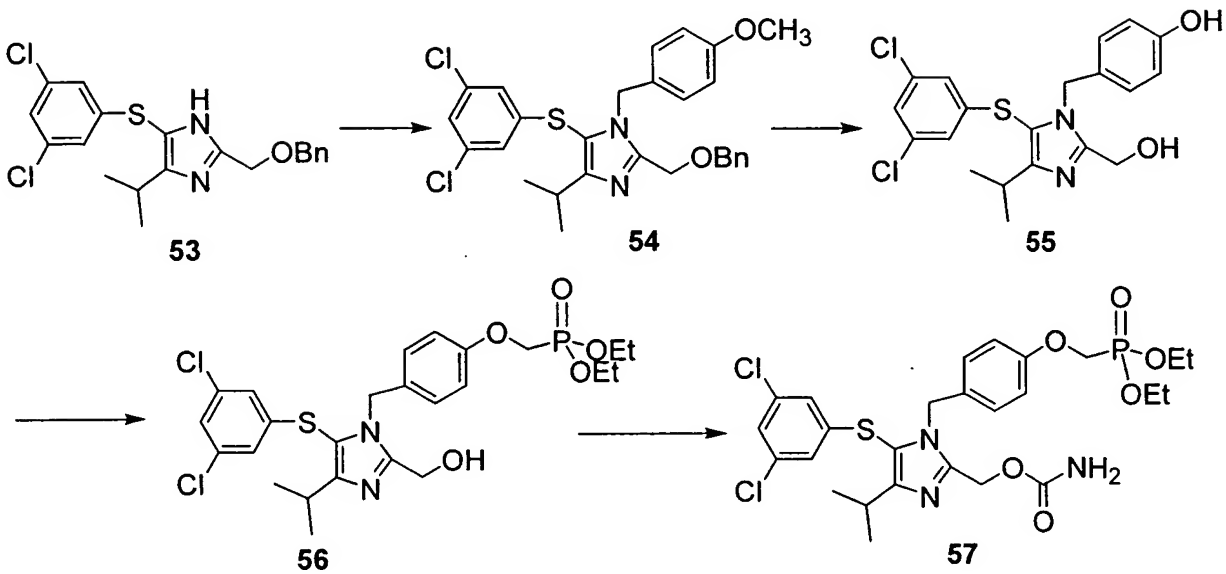
52

The title compound was prepared following the sequence of steps described in Example X21, except for substituting alanine ethyl ester for alanine n-butyl ester. Purification of the crude final product on a preparative TLC plate (5% CH_3OH/CH_2Cl_2) provided 5 mg (75%) of the title compound. ^1H NMR($CDCl_3$, 500 MHz): δ 8.46 (d, 2H), 7.32 (d, 2H), 7.20 (d, 2H), 7.15 (s, 1H), 7.05 (s, 1H), 6.82 (d, 2H), 6.70 (s, 2H), 5.27 (s, 2H), 5.19 (s, 2H), 4.12 (m, 2H), 3.70 (t, 2H), 3.19 (m, 2H), 3.12 (t, 2H), 1.48 (m, 3H), 1.47 (t, 3H), 1.25 (d,6H).

Example X23



57



Imidazole **54**: A solution of imidazole **53** (267 mg, 0.655 mmol) in THF (10 mL) was treated with 4-methoxybenzyl chloride (0.18 mL, 1.31 mmol), powder NaOH (105 mg, 2.62 mmol), lithium iodide (88 mg, 0.655 mmol), and tetrabutylammonium bromide (105 mg, 0.327 mmol). After stirring for 4 days at room temperature, the resulting mixture was partitioned between EtOAc and sat. NH_4Cl. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified on silica gel (eluting 20-40% EtOAc/hexane) to give imidazole **54** (289 mg, 84%) as a colorless oil.

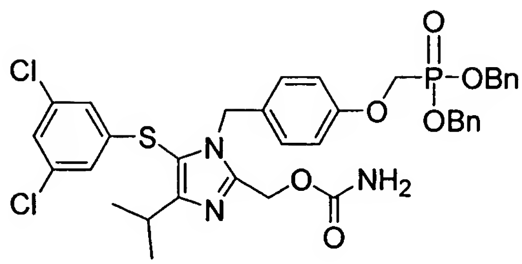
Phenol **55**: A solution of benzyl ether **54** (151 mg, 0.286 mmol) in EtOH (5 mL) was treated with conc. HCl (5 mL). After the reaction mixture was warmed to 80°C and stirred for 2 d, the mixture was concentrated under reduced pressure and partitioned between EtOAc and sat. aqueous $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified on silica gel (eluting 60-70% EtOAc/hexane) to give the alcohol (99 mg, 79%) as a colorless solid. A solution of the alcohol (77 mg, 0.18

mmol) in CH_2Cl_2 (3 mL) was added 1M BBr_3 in CH_2Cl_2 (0.90 mL, 0.90 mmol) at 0°C. After the reaction mixture was stirred for 1 h at 0°C, the mixture was neutralized with sat. $NaHCO_3$ and extracted with CH_2Cl_2 and EtOAc. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 4-5% MeOH/CH_2Cl_2) to give phenol **55** (68 mg, 89%) as a colorless solid.

Diethylphosphonate **56**: To a solution of phenol **55** (21 mg, 0.050 mmol) in CH_3CN (1 mL) and THF (1 mL) was added trifluoro-methanesulfonic acid diethoxy-phosphorylmethyl ester (18 mg, 0.060 mmol) in CH_3CN (1 mL). After the addition of Cs_2CO_3 (20 mg, 0.060 mmol), the reaction mixture was stirred for 2 h at room temperature. Additional triflate (18 mg, 0.060 mmol) and Cs_2CO_3 (20 mg, 0.060 mmol) were introduced. After the reaction mixture was stirred for another 2 h at room temperature, the mixture was concentrated under reduced pressure. The residue was partitioned between EtOAc and sat. NH_4Cl. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by preparative thin layer chromatography (eluting 5% MeOH/CH_2Cl_2) to give diethylphosphonate **56** (26 mg, 91%) as a pale yellow oil.

Title compound carbamate **57**: A solution of diethylphosphonate **56** (26 mg, 0.045 mmol) in CH_2Cl_2 (2 mL) was treated with trichloroacetyl isocyanate (27 μL, 0.23 mmol). After the reaction mixture was stirred for 10 min at room temperature, the mixture was concentrated under reduced pressure. The residue was transferred to an Al_2O_3 column in 10% MeOH/CH_2Cl_2. After soaking on the column for 30 min, the crude product was flushed out with 10% MeOH/CH_2Cl_2 and concentrated under reduced pressure. The crude product was purified by preparative thin layer chromatography eluted with 5% MeOH/CH_2Cl_2 to give title compound carbamate **57** (22 mg, 79%) as a pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.00 (s, 1H), 6.88 (d, 2H), 6.76 (d, 2H), 6.62 (s, 2H), 5.24 (s, 2H), 5.18 (s, 2H), 4.26 (q, 4H), 4.21 (d, 2H), 3.15 (m, 1H), 1.38 (t, 6H), 1.29 (d, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 19.1.

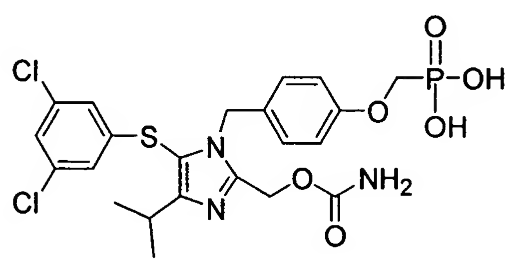
ExampleX24



58

The title compound **58** was prepared following the sequence of steps described in Example X23 with substitution of trifluoro-methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester for trifluoro-methanesulfonic acid diethoxy-phosphorylmethyl ester. Purification of the crude final product on silica gel eluted with 3-4% $MeOH/CH_2Cl_2$ provided 33 mg of the title compound. ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (m, 10H), 6.96 (s, 1H), 6.85 (d, 2H), 6.70 (d, 2H), 6.62 (s, 2H), 5.23 (s, 2H), 5.17 (s, 2H), 5.13 (m, 4H), 4.18 (d, 2H), 3.16 (m, 1H), 1.30 (d, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 20.1.

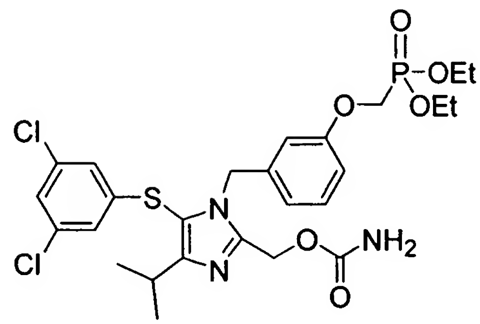
Example X25



59

A solution of dibenzylphosphonate **58** (15 mg, 0.020 mmol) was treated 4M HCl in dioxane (1 mL). After the reaction mixture was stirred for 18 h at room temperature, the mixture was concentrated under reduced pressure. The crude product was purified on a C-18 column (eluting 30-40% CH_3CN/H_2O) to give phosphonic acid **59** (8 mg, 71%) as a colorless oil. ^1H NMR (300 MHz, CD_3OD) δ 7.19 (s, 1H), 7.08 (d, 2H), 6.81 (d, 2H), 6.69 (s, 2H), 5.48 (s, 2H), 5.44 (s, 2H), 4.12 (d, 2H), 3.32 (m, 1H), 1.33 (d, 6H). ^{31}P NMR (300 MHz, CD_3OD) δ 17.1.

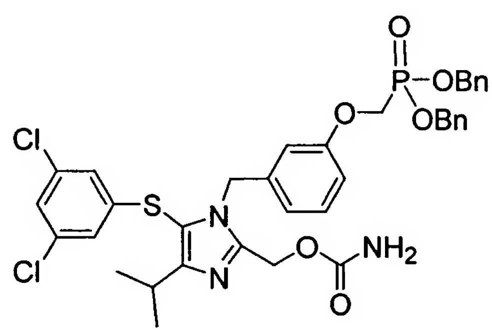
Example X26



60

The title compound **60** was prepared following the sequence of steps described in Example X23, except for substituting 3-methoxy benzyl chloride for 4-methoxybenzyl chloride. Purification of the crude final product on preparative thin layer chromatography eluted with 5% $MeOH/CH_2Cl_2$ provided 28 mg of the title compound. ^1H NMR (500 MHz, $CDCl_3$) δ 7.12 (t, 1H), 7.03 (s, 1H), 6.75 (d, 1H), 6.66 (s, 2H), 6.60 (d, 1H), 6.55 (s, 1H), 5.24 (s, 2H), 5.19 (s, 2H), 4.22 (q, 4H), 4.20 (d, 2H), 3.17 (m, 1H), 1.37 (t, 6H), 1.31 (d, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 19.2.

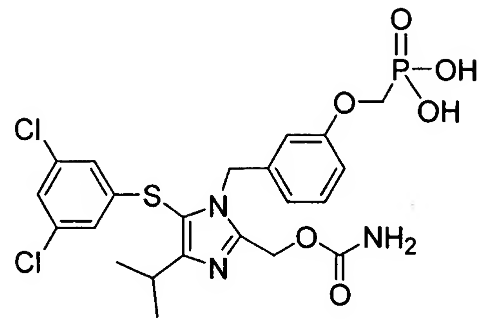
Example X27



61

The title compound **61** was prepared following the sequence of steps described in Example X24, except for substituting 3-methoxybenzyl chloride for 4-methoxybenzyl chloride. Purification of the crude final product on silica gel eluted with 3-4% $MeOH/CH_2Cl_2$ provided 36 mg of the title compound. ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (m, 10H), 7.10 (t, 1H), 7.00 (s, 1H), 6.68 (d, 1H), 6.64 (s, 2H), 6.59 (d, 1H), 6.53 (s, 1H), 5.23 (s, 2H), 5.17 (s, 2H), 5.11 (m, 4H), 4.18 (d, 2H), 3.16 (m, 1H), 1.31 (d, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 20.2.

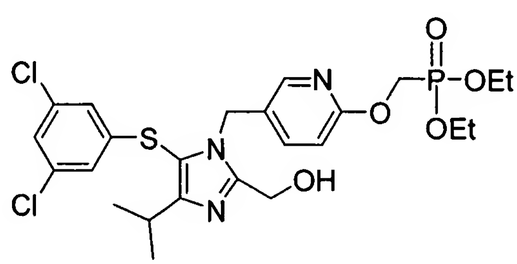
Example X28



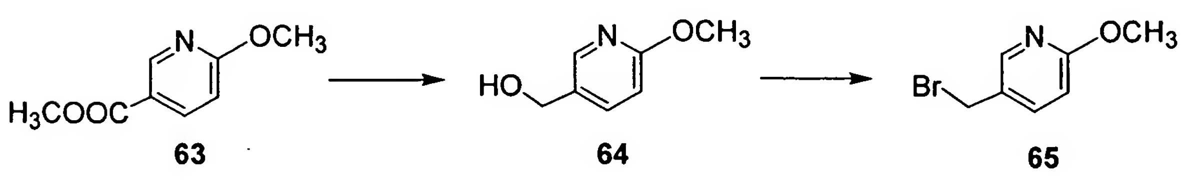
62

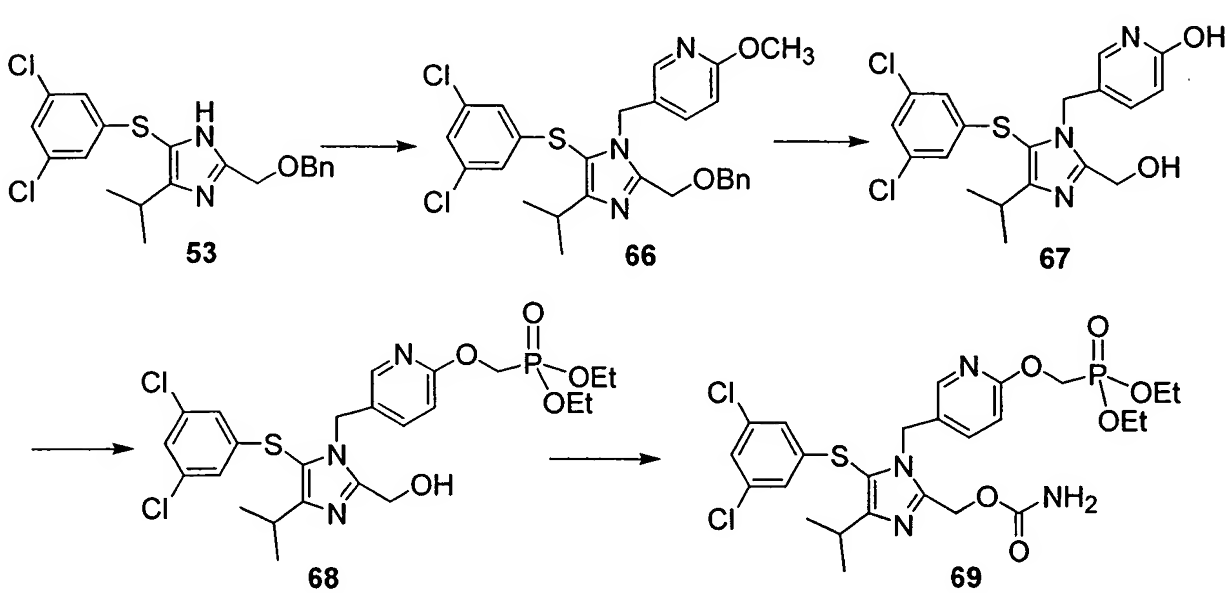
The title compound **62** was prepared following the sequence of steps described in Example X25, except for substituting compound **61** for compound 58. Purification of the crude final product with HPLC (eluting 30-40% CH_3CN/H_2O) provided 7 mg of the title compound. ^{1}H NMR (300 MHz, CD_3OD) δ 7.18 (s, 1H), 7.13 (t, 1H), 6.81 (d, 1H), 6.77 (s, 2H), 6.72 (s, 1H), 6.68 (d, 1H), 5.49 (s, 2H), 5.37 (s, 2H), 4.12 (d, 2H), 3.33 (m, 1H), 1.34 (d, 6H). ^{31}P NMR (300 MHz, CD_3OD) δ 17.0.

Example X29



68





Alcohol **64**: A solution of methyl 6-methoxynicotinate **63** (2.0 g, 12 mmol) in Et_2O (50 mL) was treated with 1.5M DIBAL-H in toluene (16.8 mL, 25.1 mmol) at 0°C. After the reaction mixture was stirred for 1 h at 0°C, the mixture was quenched with 1M sodium potassium tartrate and stirred for an additional 2 h. The aqueous phase was extracted with Et_2O and concentrated to give alcohol **64** (1.54 g, 92%) as a pale yellow oil.

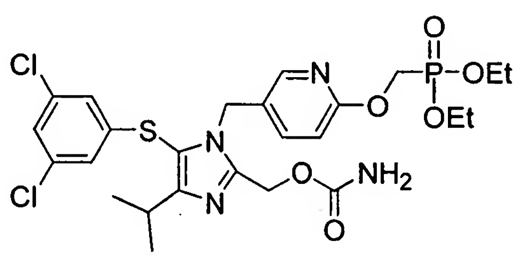
Bromide **65**: A solution of alcohol **64** (700 mg, 5.0 mmol) in CH_2Cl_2 (50 mL) was treated with carbon tetrabromide (2.49 g, 7.5 mmol) and triphenylphosphine (1.44 g, 5.5 mmol) at 0°C. After the reaction mixture was stirred for 30 min at room temperature, the mixture was partitioned between CH_2Cl_2 and sat. aqueous $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified on silica gel (eluting 5-10% $MeOH/CH_2Cl_2$) to give bromide **65** (754 mg, 75%) as colorless crystals.

Imidazole **66**: A solution of imidazole **53** (760 mg, 1.86 mmol) and bromide **65** (752 mg, 3.72 mmol) in THF (10 mL) was treated with powder NaOH (298 mg, 7.44 mmol), lithium iodide (249 mg, 1.86 mmol), and tetrabutylammonium bromide (300 mg, 0.93 mmol). After stirring for 14 h at room temperature, the mixture was partitioned between EtOAc and sat. NH_4Cl. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified on silica gel (eluting 20-30% EtOAc/hexane) to give imidazole **66** (818 mg, 83%) as a pale yellow oil.

Diol **67**: A solution of benzyl ether **66** (348 mg, 0.658 mmol) in EtOH (3 mL) was treated with conc. HCl (3 mL). After the reaction mixture was warmed to 80°C and stirred for 18 h, the mixture was concentrated under reduced pressure. The crude product was chromatographed on silica gel (eluting 5-10% $MeOH/CH_2Cl_2$) to give diol **67** (275 mg, 98%) as a colorless solid.

Title compound diethylphosphonate **68**: A solution of diol **67** (40 mg, 0.094 mmol) in THF (1 mL) was treated with trifluoro-methanesulfonic acid diethoxy-phosphorylmethyl ester (114 mg, 0.38 mmol) in THF (1 mL). After the addition of Ag_2CO_3 (52 mg, 0.19 mmol), the reaction mixture was stirred for 5 d at room temperature. The mixture was quenched with sat. $NaHCO_3$ and sat. NaCl, and extracted with EtOAc. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed by silica gel (eluting 3-4% $MeOH/CH_2Cl_2$) and by preparative thin layer chromatography (eluting 4% $MeOH/CH_2Cl_2$) to give the title compound diethylphosphonate **68** (23 mg, 43%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.39 (d, 1H), 7.00 (s, 1H), 6.65 (d, 1H), 6.55 (d, 2H), 5.20 (s, 2H), 4.81 (s, 2H), 4.55 (d, 2H), 4.21 (m, 4H), 3.08 (m, 1H), 1.35 (t, 6H), 1.20 (d, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 20.7.

<u>Example X30</u>

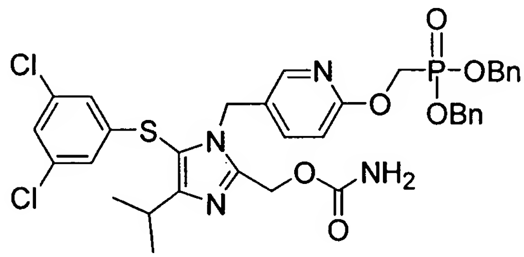


69

A solution of diethylphosphonate **68** (13 mg, 0.023 mmol) in CH_2Cl_2 (0.5 mL) was treated with trichloroacetyl isocyanate (13 μL, 0.11 mmol). After the reaction mixture was stirred for 10 min at room temperature, the mixture was concentrated under reduced pressure. The residue was transferred to an Al_2O_3 column in 10% $MeOH/CH_2Cl_2$. After soaking on the column for 30 min, the crude product was flushed out with 10% $MeOH/CH_2Cl_2$ and concentrated under reduced pressure. The crude product was purified by preparative thin layer chromatography (eluting 5% $MeOH/CH_2Cl_2$) to give carbamate **69** (13 mg, 92%) as a pale

yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, 1H), 7.20 (dd, 1H), 7.03 (t, 1H), 6.65 (d, 1H), 6.62 (d, 2H), 5.24 (s, 2H), 5.16 (s, 2H), 4.74 (bs, 2H), 4.58 (d, 2H), 4.20 (m, 4H), 3.13 (m, 1H), 1.35 (t, 6H), 1.27 (d, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 20.7.

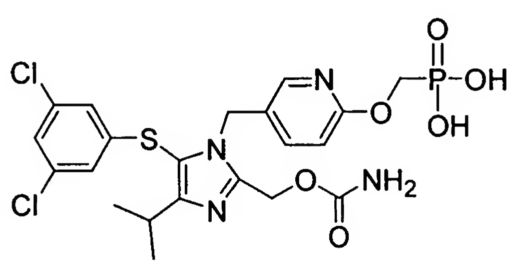
Example X31



70

The title compound **70** was prepared following the sequence of steps described in Example X29, except for substituting trifluoro-methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester for trifluoro-methanesulfonic acid diethoxy-phosphorylmethyl ester. Purification of the crude final product on silica gel eluted with 50-60% CH_3CN/H_2O provided 12 mg of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.34 (m, 10H), 7.19 (dd, 1H), 7.02 (t, 1H), 6.63 (s, 1H), 6.61 (d, 2H), 5.38 (s, 2H), 5.25 (s, 2H), 5.11 (m, 4H), 4.62 (d, 2H), 3.24 (m, 1H), 1.33 (d, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 21.4.

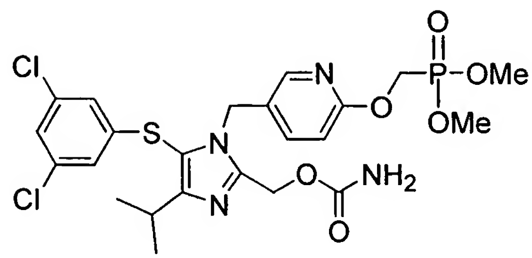
Example X32



71

The title compound **71** was prepared following the sequence of steps described in Example X25, except for substituting compound **70** for compound **28**. Purification of the crude final product with HPLC provided 2 mg of the title compound. ^{1}H NMR (300 MHz, CD_3OD) δ 7.90 (s, 1H), 7.44 (d, 1H), 7.13 (t, 1H), 6.72 (m, 3H), 5.39 (s, 2H), 5.34 (s, 2H), 4.39 (d, 2H), 3.30 (m, 1H), 1.28 (d, 6H).

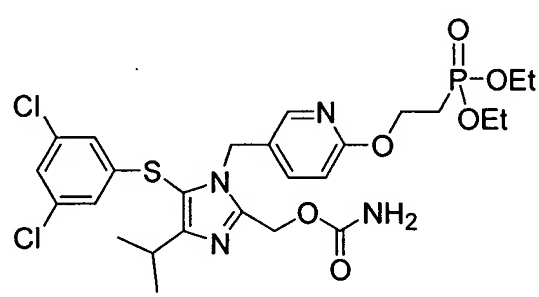
Example X33



72

To a solution of phosphonic acid **72** (33 mg, 0.058 mmol) in DMF (2 mL) was added benzotriazol-1-yloxytripyrrolidino-phosphonium hexafluorophosphate (91 mg, 0.175 mmol), iPr_2NEt (30 μL, 0.175 mmol), and MeOH (0.24 mL, 5.83 mmol). After the reaction mixture was stirred for 2 d at room temperature, the mixture was partitioned between EtOAc and sat. NH_4Cl. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification of the crude final product on silica gel eluted with 3-5% $MeOH/CH_2Cl_2$ and by preparative thin layer chromatography (eluting 5% $MeOH/CH_2Cl_2$) provided 6 mg of the title compound as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, 1H), 7.21 (dd, 1H), 7.04 (s, 1H), 6.66 (d, 1H), 6.62 (d, 2H), 5.25 (s, 2H), 5.17 (s, 2H), 4.70 (bs, 2H), 4.63 (d, 2H), 3.84 (d, 6H), 3.14 (m, 1H), 1.28 (d, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 23.2.

Example X34

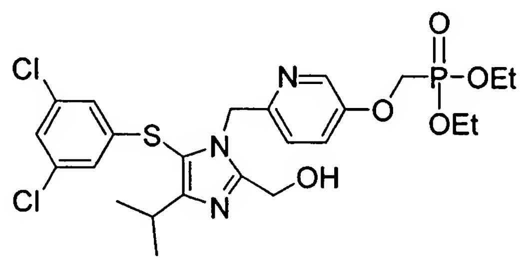


73

A solution of diol **67** (50 mg, 0.118 mmol) in CH_2Cl_2 (5 mL) was treated with diethyl (2-bromoethyl)-phosphonate (64 μL, 0.354 mmol) and Ag_2CO_3 (65 mg, 0.236 mmol). After the reaction mixture was stirred for 3 d at 40°C, additional phosphonate (64 μL, 0.354 mmol), Ag_2CO_3 (65 mg, 0.236 mmol), and benzene (5 mL) were introduced. After the reaction mixture was stirred for another 4 days at 70°C, the mixture was filtered through a medium-fritted funnel.

The crude product was chromatographed by silica gel (eluting 4-5% MeOH/CH_2Cl_2) to give diethylphosphonate **74** (8 mg, 12%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (bs, 1H), 7.17 (dd, 1H), 7.03 (t, 1H), 6.60 (d, 2H), 6.52 (d, 2H), 5.25 (s, 2H), 5.15 (s, 2H), 4.71 (bs, 2H), 4.47 (m, 2H), 4.14 (m, 4H), 3.12 (m, 1H), 2.27 (m, 2H), 1.34 (t, 6H), 1.27 (d, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 28.0.

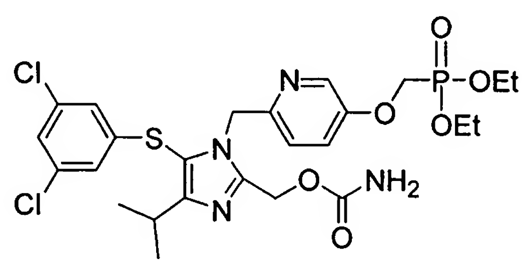
Example X35



74

The title compound **74** was prepared following the sequence of steps described in Example X29, except for substituting 6-bromomethyl-3-methoxy pyridine for 5-bromomethyl-2-methoxy pyridine **65**. Purification of the crude final product on silica gel with 4-5% MeOH/CH_2Cl_2 provided 66 mg of the title compound. ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, 1H), 7.01 (d, 1H), 6.93 (m, 2H), 6.41 (d, 2H), 5.26 (s, 2H), 4.94 (s, 2H), 4.22 (q, 4H), 4.12 (m, 2H), 3.08 (m, 1H), 1.38 (t, 6H), 1.25 (d, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 17.7.

Example X36

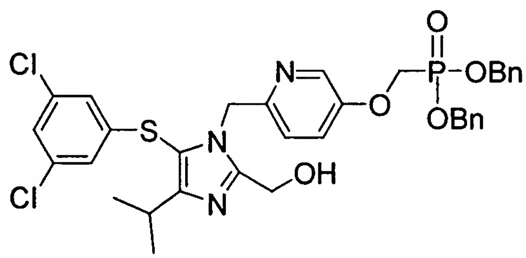


75

The title compound **75** was prepared following the sequence of steps described in Example X30, except for substituting compound **74** for compound **68**. Purification of the crude final product on preparative thin layer chromatography eluted with 5% MeOH/CH_2Cl_2 provided 15 mg the title compound. ^1H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, 1H), 6.98 (m, 1H), 6.96 (m,

1H), 6.79 (d, 1H), 6.58 (d, 2H), 5.35 (s, 2H), 5.32 (s, 2H), 4.83 (bs, 2H), 4.25 (q, 4H), 4.24 (m, 2H), 3.14 (m, 1H), 1.39 (t, 6H), 1.28 (d, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 18.1.

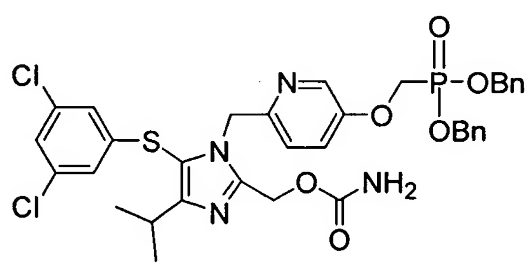
Example X37



76

The title compound **76** was prepared following the sequence of steps described in Example X35, except for substituting trifluoro-methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester for trifluoro-methanesulfonic acid diethoxy-phosphorylmethyl ester. Purification of the crude final product on silica gel eluted with 4% MeOH/CH_2Cl_2 provided 67 mg of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, 1H), 7.36 (m, 10H), 6.95 (d, 1H), 6.81 (m, 2H), 6.37 (d, 2H), 5.22 (s, 2H), 5.13 (m, 4H), 4.91 (s, 2H), 4.11 (d, 2H), 3.05 (m, 1H), 1.22 (d, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 18.8.

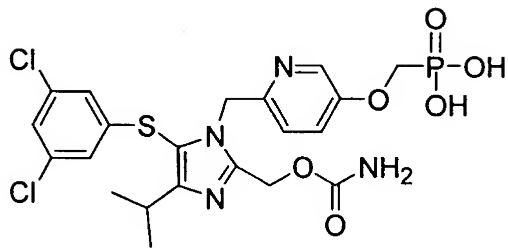
Example X38



77

The title compound **77** was prepared following the sequence of steps described in Example X30, except for substituting compound **76** for compound **68**. Purification of the crude final product on silica gel eluted with 4-5% MeOH/CH_2Cl_2 provided 35 mg of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, 1H), 7.36 (m, 10H), 6.85 (m, 2H), 6.72 (d, 1H), 6.55 (d, 2H), 5.35 (s, 2H), 5.29 (s, 2H), 5.13 (m, 4H), 4.74 (bs, 2H), 4.15 (d, 2H), 3.13 (m, 1H), 1.28 (d, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 19.2.

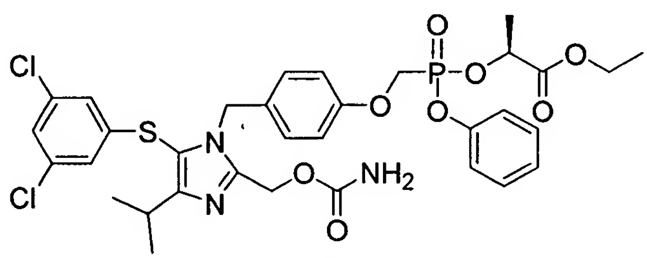
Example X39



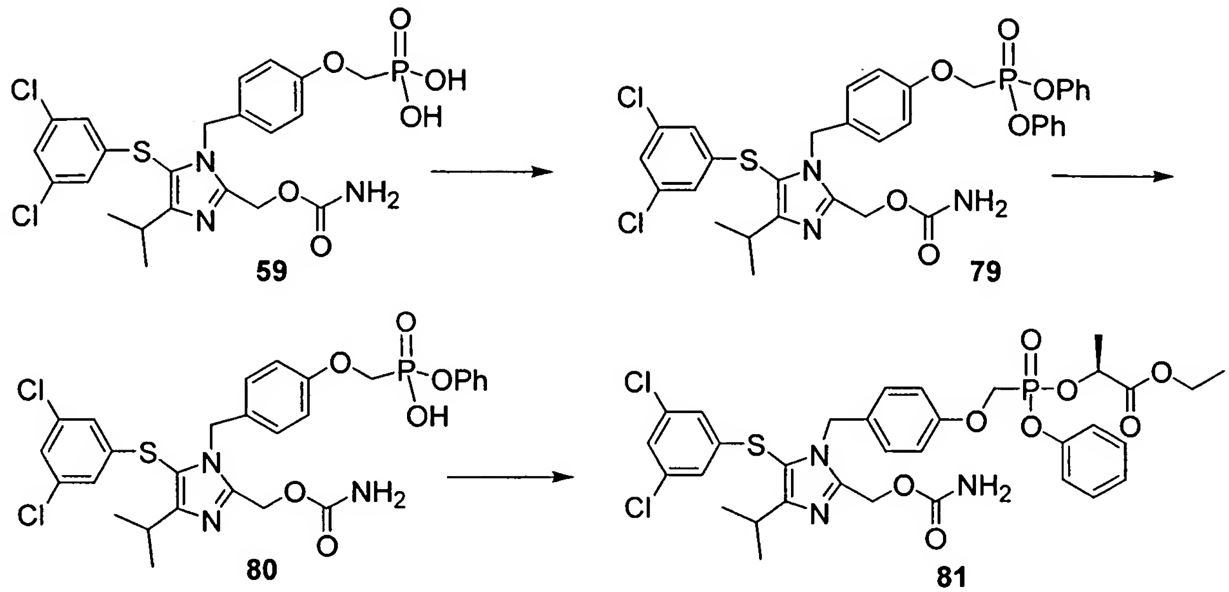
78

The title compound **78** was prepared following the sequence of steps described in Example X25, except for substituting compound **77** for compound **58**. Purification of the crude final product on a C-18 column eluted with 30% CH_3CN/H_2O provided 6 mg of the title compound. ^1H NMR (300 MHz, CD_3OD) δ 8.16 (bs, 1H), 7.21 (bs, 2H), 7.18 (bs, 1H), 6.70 (d, 2H), 5.64 (s, 2H), 5.49 (s, 2H), 4.21 (d, 2H), 3.34 (m, 1H), 1.34 (d, 6H). ^{31}P NMR (300 MHz, CD_3OD) δ 16.0.

Example X40



81



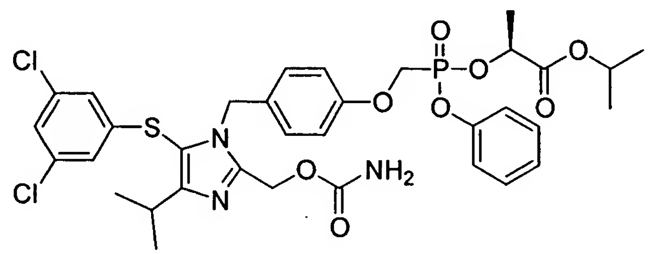
Diphenylphosphonate **79**: A solution of phosphonic acid **59** (389 mg, 0.694 mmol) in pyridine (5 mL) was treated with phenol (653 mg, 6.94 mmol) and 1,3-dicyclohexylcarbodiimide (573 mg, 2.78 mmol). After stirring at 70°C for 2 h, the mixture was diluted with CH_3CN and filtered through a fritted funnel. The filtrate was partitioned between EtOAc and sat. NH_4Cl, and extracted with EtOAc. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified on silica gel (eluting 60-80% EtOAc/hexane) to give diphenylphosphonate **79** (278 mg, 56%) as a colorless oil.

Phosphonic acid **80**: A solution of diphenylphosphonate **79** (258 mg, 0.362 mmol) in CH_3CN (20 mL) was treated with 1N NaOH (0.72 mL, 0.724 mmol) at 0°C. After the reaction mixture was stirred for 3 h at 0°C, the mixture was filtered through Dowex 50WX8-400 acidic resin (380 mg), rinsed with MeOH, and concentrated under reduced pressure to give phosphonic acid **80** (157 mg, 68%) as a colorless solid.

Title compound **81**: A solution of phosphonic acid **80** (35 mg, 0.055 mmol) in CH_3CN (1 mL) and THF (1 mL) was treated with thionyl chloride (12 μL, 0.16 mmol). After the reaction mixture was warmed to 70°C and stirred for 2 h, the mixture was concentrated under reduced pressure. The residue was then dissolved in CH_2Cl_2 (2 mL) and cooled to 0°C. Triethylamine (31 μL, 0.22 mmol) and ethyl S-(-)-lactate (19 μL, 0.16 mmol) were added. After stirring for 1 h at 0°C and 1 h at room temperature, the reaction mixture was neutralized with sat. NH_4Cl and extracted with CH_2Cl_2 and EtOAc. The organic phase was dried over Na_2SO_4, filtered, and

evaporated under reduced pressure. The crude product was purified by preparative thin layer chromatography (eluting 70% EtOAc/hexane) to give ethyl lactate **81** (7 mg, 17%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 6.99 (d, 1H), 6.82 (m, 4H), 6.63 (d, 2H), 5.23 (s, 2H), 5.18 (s, 2H), 5.14 (m, 1H), 4.67 (bs, 2H), 4.51 (d, 2H), 4.20 (m, 2H), 3.16 (m, 1H), 1.61 (d, 1.5H), 1.50 (d, 1.5H), 1.30 (d, 6H), 1.24 (m, 3H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 17.0, 15.0.

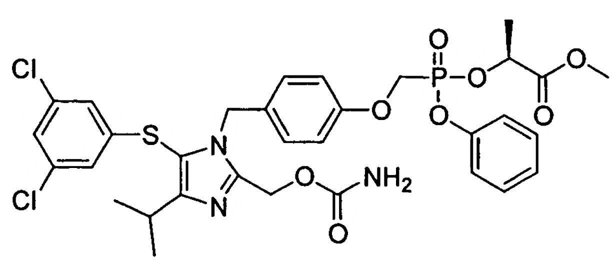
Example X41



82

The title compound **82** was prepared following the sequence of steps described in Example X40, except for reacting monophosphonic acid **80** with isopropyl lactate. Purification of the crude final product on silica gel eluted with 70-90% EtOAc/hexane provided 5.4 mg of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 3H), 7.25 (m, 3H), 7.0 (s, 0.5H), 6.98 (s, 0.5H), 6.86 (m, 2H), 6.79 (m, 2H), 6.64 (s, 1H), 6.61 (s, 1H), 5.22 (s, 2H), 5.17 (s, 2H), 5.06 (b, 1H), 4.62 (b, 2H), 4.53 (m, 2H), 4.38 (q, 1H), 3.15 (m, 1H), 1.60 (d, 1.5H), 1.48 (d, 1.5H), 1.30 (d, 3H), 1.28 (d, 3H), 1.20 (d, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 17.04, 14.94 (1:1 diastereomeric ratio).

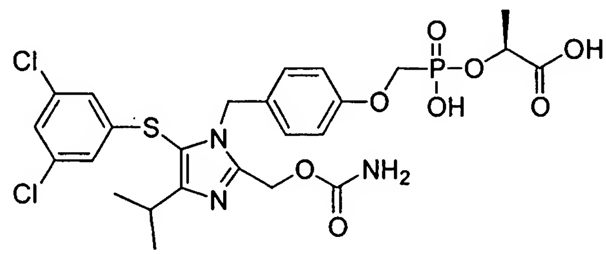
Example X42



83

The title compound **83** was prepared following the sequence of steps described in Example X40, except for reacting monophosphonic acid **80** with methyl lactate. Purification of the crude final product on silica gel eluted with 70-90% EtOAc/hexane provided 2.7 mg of the title compound. ^{1}H NMR (300 MHz, CD_3CN) δ 7.40 (m, 2H), 7.25 (m, 3H), 7.08 (s, 1H), 6.98 (d, 2H), 6.77 (d, 2H), 6.64 (s, 2H), 5.20 (s, 2H), 5.16 (s, 2H), 5.13 (b, 1H), 4.47 (m, 2H), 3.72 (s, 2H), 3.67 (s, 1H), 3.09 (m, 1H), 1.56 (d, 1H), 1.51 (d, 2H), 1.20 (d, 6H). ^{31}P NMR (300 MHz, CD_3CN) δ 16.86, 15.80 (2.37:1 diastereomeric ratio).

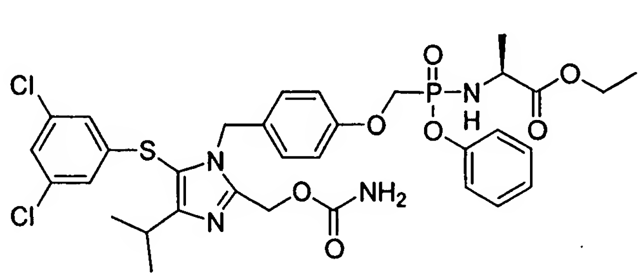
Example X43



84

A solution of mono-lactate phosphonate compound **83** (131 mg, 0.18 mmol) in DMSO/MeCN (1 mL/2 mL) and PBS buffer (10 mL) was treated with esterase (400 μL). After the reaction mixture was warmed to 40°C and stirred for 7 days, the mixture was filtered and concentrated under reduced pressure. Purification of the crude product on C_{18} column eluted with MeCN/H_2O provided 17.3 mg (15 %) of the title compound **84**. ^{1}H NMR (300 MHz, CD_3OD) δ 7.20 (s, 1H), 7.02 (d, 2H), 6.79 (d, 2H), 6.71 (s, 2H), 5.40 (s, 2H), 5.35 (s, 2H), 5.34 (b, 1H) 4.10 (bd, 2H), 3.26 (m, 1H), 1.50 (d, 3H), 1.30 (d, 6H). ^{31}P NMR (300 MHz, CD_3OD) δ 14.2.

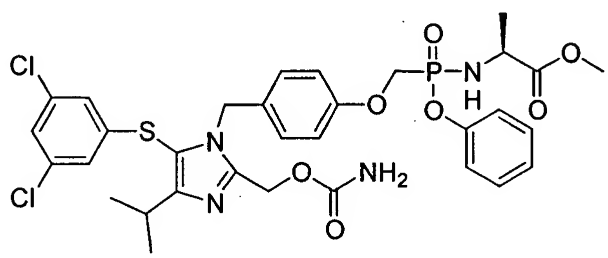
Example X44



85

The title compound **85** was prepared following the sequence of steps described in Example X40, except for reacting monophosphonic acid **80** with L-alanine ethyl ester. Purification of the crude final product on preparative thin layer chromatography eluted with 80% EtOAc/hexane provided 7 mg of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 5H), 6.98 (d, 1H), 6.87 (d, 2H), 6.73 (t, 2H), 6.62 (s, 2H), 5.21 (s, 2H), 5.17 (s, 2H), 4.28 (bs, 2H), 4.25 (m, 2H), 4.10 (m, 2H), 4.02 (m, 1H), 3.66 (m, 1H), 3.14 (m, 1H), 1.28 (d, 6H), 1.24 (m, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 20.2, 19.1.

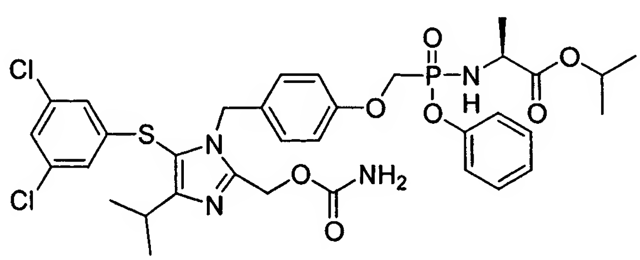
Example X45



86

The title compound **86** was prepared following the sequence of steps described in Example X40, except for reacting monophosphonic acid **80** with L-alanine methyl ester. Purification of the crude final product on preparative thin layer chromatography eluted with 80% EtOAc/hexane provided 8 mg of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5H), 6.98 (d, 1H), 6.88 (d, 2H), 6.73 (t, 2H), 6.61 (bs, 2H), 5.21 (d, 2H), 5.17 (s, 2H), 4.66 (bs, 2H), 4.25 (m, 3H), 3.66 (s, 1.5H), 3.64 (m, 1H), 3.59 (m, 1.5H), 3.14 (m, 1H), 1.36 (t, 6H), 1.28 (d, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 20.2, 19.0.

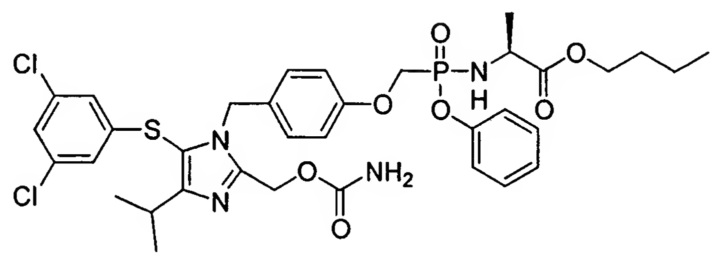
Example X46



87

The title compound **87** was prepared following the sequence of steps described in Example X40, except for reacting monophosphonic acid **80** with L-alanine isopropyl ester. Purification of the crude final product on preparative thin layer chromatography eluted with 80% EtOAc/hexane provided 7 mg of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5H), 6.98 (m, 1H), 6.87 (d, 2H), 6.74 (m, 2H), 6.61 (bs, 2H), 5.22 (d, 2H), 5.18 (s, 2H), 4.93 (m, 1H), 4.68 (bs, 2H), 4.25 (m, 3H), 3.66 (s, 1H), 3.15 (m, 1H), 1.34 (m, 3H), 1.29 (d, 6H), 1.17 (m, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 20.1, 19.1.

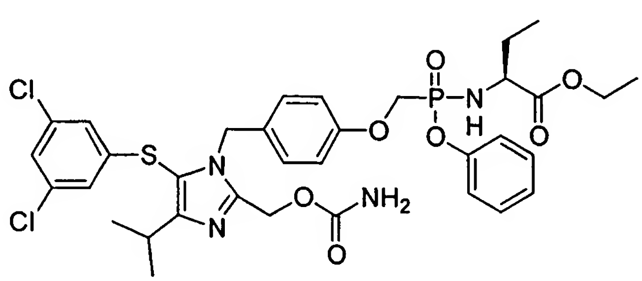
Example X47



88

The title compound **88** was prepared following the sequence of steps described in Example X40, except for reacting monophosphonic acid **80** with L-alanine *n*-butyl ester. Purification of the crude final product on preparative thin layer chromatography eluted with 80% EtOAc/hexane provided 6 mg of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5H), 6.98 (bd, 1H), 6.88 (d, 2H), 6.73 (t, 2H), 6.61 (d, 2H), 5.22 (d, 2H), 5.17 (s, 2H), 4.63 (bs, 2H), 4.25 (m, 3H), 4.06 (m, 2H), 3.65 (m, 1H), 3.14 (m, 1H), 1.58 (m, 4H), 1.36 (m, 3H), 1.28 (d, 6H), 0.90 (t, 3H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 20.2, 19.1.

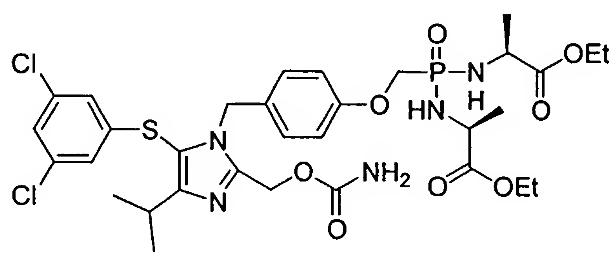
Example X48



89

The title compound **89** was prepared following the sequence of steps described in Example X40, except for reacting monophosphonic acid **80** with L-alanine *n*-butyl ester. Purification of the crude final product on preparative thin layer chromatography eluted with 80% EtOAc/hexane provided 4 mg of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (m, 5H), 6.98 (m, 1H), 6.87 (d, 2H), 6.74 (t, 2H), 6.62 (d, 2H), 5.21 (d, 2H), 5.17 (s, 2H), 4.64 (bs, 2H), 4.24 (m, 2H), 4.11 (m, 3H), 3.58 (m, 1H), 3.15 (m, 1H), 1.28 (d, 6H), 1.19 (m, 5H), 0.84 (m, 3H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 20.4, 19.4.

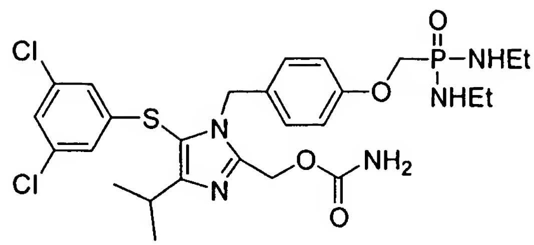
Example X49



90

To a solution of phosphonic acid **59** (61 mg, 0.11 mmol) in DMF (1 mL) was added benzotriazol-1-yloxytripyrrolidino-phosphonium hexafluorophosphate (169 mg, 0.32 mmol), L-alanine ethyl ester (50 mg, 0.32 mmol), and DIEA (151 μL, 0.87 mmol). The reaction mixture was stirred for 5 hours at room temperature. Then the mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with HCl (5 % aq), and extracted with EtOAc (3x). The organic phase was washed with sat. $NaHCO_3$, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was purified on silica gel eluted with 5-8% MeOH/CH_2Cl_2 to give 5.5 mg of compound bis-amidate **90** as white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.88 (d, 2H), 6.73 (d, 2H), 6.62 (s, 2H), 5.23 (s, 2H), 5.17 (s, 2H), 4.70 (bs, 2H), 4.25 (bm, 8H), 3.40 (q, 2H), 3.16 (m, 1H), 1.44 (t, 6H), 1.24 (d, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 19.41.

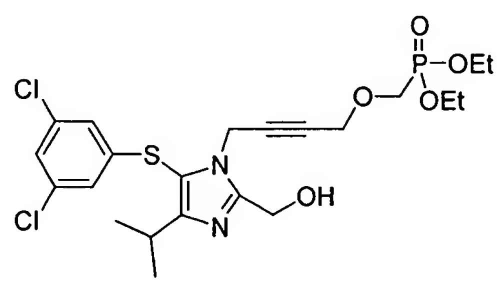
Example X50



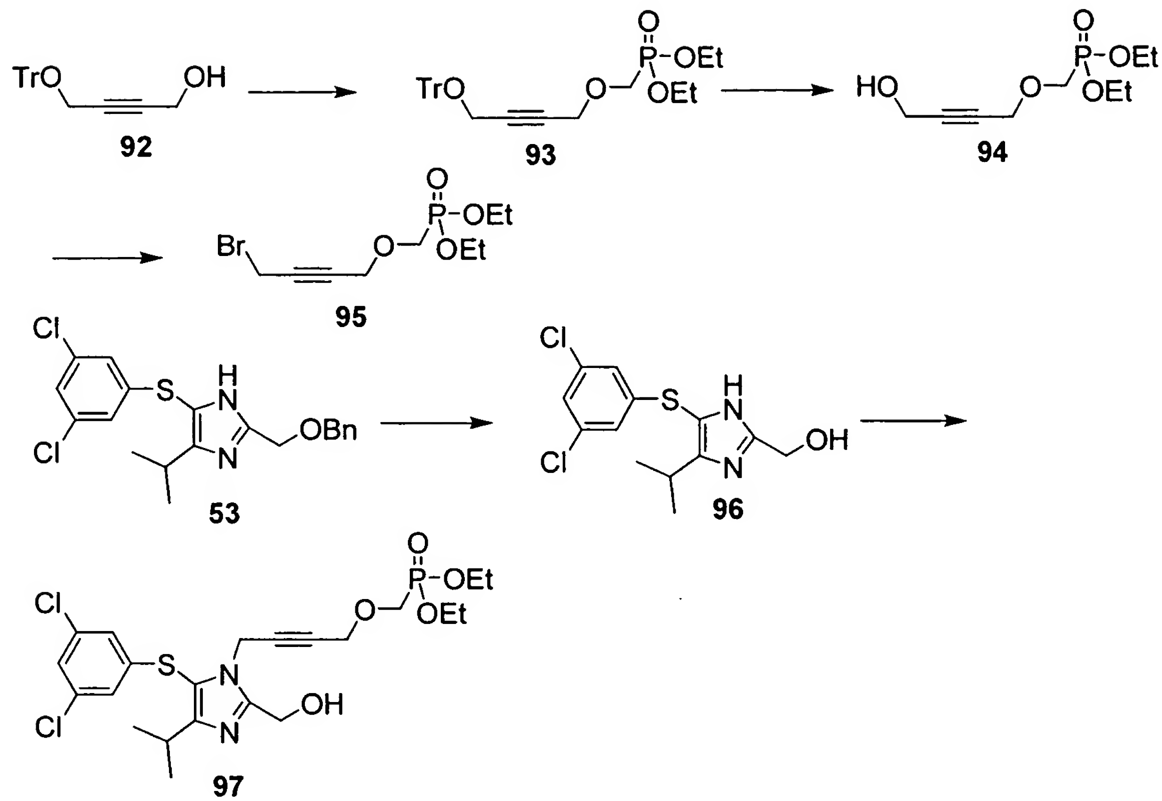
91

The title compound **91** was prepared following the sequence of steps described in Example X49, except for substituting ethyl amine for L-alanine ethyl ester. Purification of the crude final product on silica gel eluted with 4-10% $MeOH/CH_2Cl_2$ provided 14.8 mg of the title compound. ^{1}H NMR (300 MHz, CD_3OD) δ 7.07 (s, 1H), 6.99 (d, 2H), 6.77 (d, 2H), 6.60 (s, 2H), 5.27 (s, 2H), 5.22 (s, 2H), 4.07 (d, 2H), 3.09 (m, 1H), 3.01 (bm, 4H), 1.24 (d, 6H), 1.16 (t, 6H). ^{31}P NMR (300 MHz, CD_3OD) δ 24.66.

Example X51



97



Diethylphosphonate **93**: A solution of alcohol **92** (200 mg, 0.609 mmol) in THF (5 mL) was treated with 60% NaH in mineral oil (37 mg, 0.914 mmol) at 0°C. After the reaction mixture was stirred for 5 min at 0°C, trifluoro-methanesulfonic acid diethoxy-phosphorylmethyl ester (219 mg, 0.731 mmol) was added in THF (3 mL). After the reaction mixture was stirred for an additional 30 min, the mixture was quenched with sat. NH_4Cl and extracted with EtOAc. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give crude diethylphosphonate **93** as a colorless oil.

Alcohol **94**: A solution of diethylphosphonate **93** (291 mg, 0.609 mmol) in CH_2Cl_2 (5 mL) was treated with trifluoroacetic acid (0.5 mL). After the reaction mixture was stirred for 30 min at room temperature, the mixture was concentrated under reduced pressure. The crude product was purified on silica gel (eluting 4-5% $MeOH/CH_2Cl_2$) to give alcohol **94** (135 mg, 94% over 2 steps) as a colorless oil.

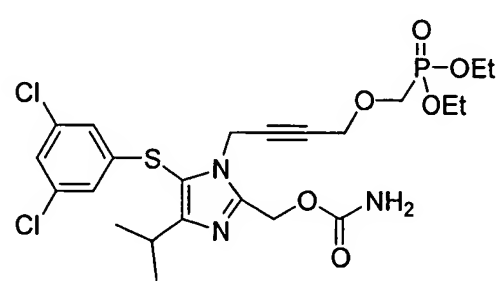
Bromide **95**: A solution of alcohol **94** (134 mg, 0.567 mmol) in CH_2Cl_2 (5 mL) was treated with carbon tetrabromide (282 mg, 0.851 mmol) and triphenylphosphine (164 mg, 0.624 mmol). After stirring at room temperature for 1 h, the mixture was partitioned between CH_2Cl_2 and sat. $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered, and evaporated under

reduced pressure. The crude product was purified twice on silica gel (eluting 60-100% EtOAc/hexane, followed by eluting 0-2% $MeOH/CH_2Cl_2$) to give bromide **95** (80 mg, 47%) as a colorless oil.

Imidazole **96**: A solution of benzyl ether **53** (2.58 g, 6.34 mmol) in EtOH (60 mL) was treated with conc. HCl (60 mL). After the reaction mixture was warmed to 100°C and stirred for 18 h, the mixture was concentrated under reduced pressure. The residue was partitioned between EtOAc and sat. $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 8-9% $MeOH/CH_2Cl_2$) to give imidazole **96** (1.86 g, 93%) as a colorless solid.

Title compound **97**: A solution of imidazole **96** (54 mg, 0.170 mmol) and bromide **95** (56 mg, 0.187 mmol) in THF (3 mL) was treated with powder NaOH (14 mg, 0.340 mmol), lithium iodide (23 mg, 0.170 mmol), and tetrabutylammonium bromide (27 mg, 0.085 mmol) were then added. After stirring at room temperature for 2 h, the mixture was partitioned between EtOAc and sat. NH_4Cl. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified on silica gel (eluting 3-4% $MeOH/CH_2Cl_2$) and by preparative thin layer chromatography (eluting 5% $MeOH/CH_2Cl_2$) to give alcohol **97** (42 mg, 46%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (bs, 1H), 6.86 (d, 2H), 4.92 (s, 2H), 4.87 (s, 2H), 4.16 (m, 6H), 3.73 (d, 2H), 3.10 (m, 1H), 1.34 (t, 6H), 1.21 (d, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 20.8.

Example X52

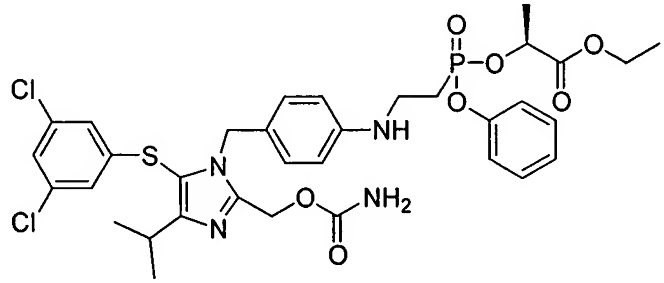


97a

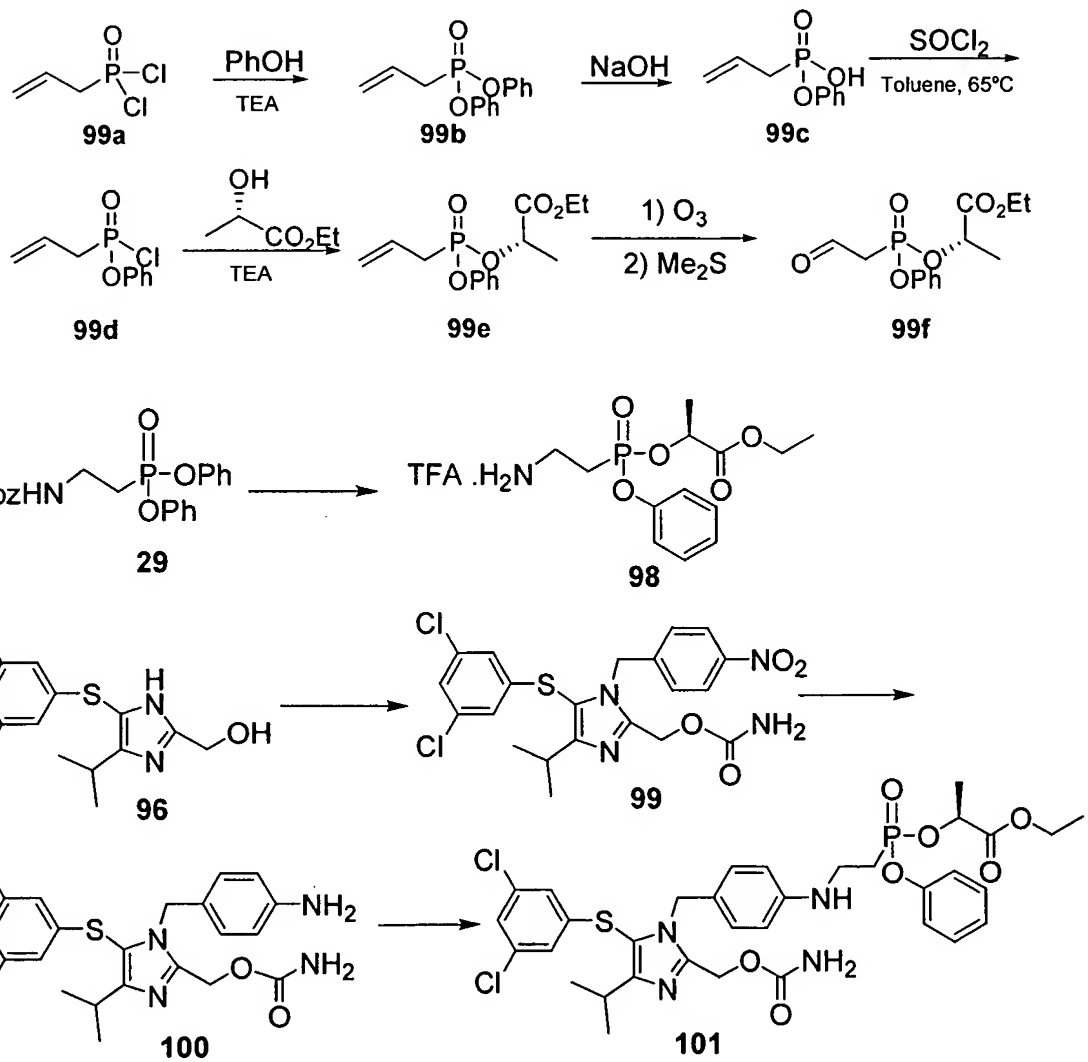
The title compound **97a** was prepared following the sequence of steps described in Example X29 by substituting compound **97** for compound **68**. Purification of the crude final product on silica gel eluted with 3-4% $MeOH/CH_2Cl_2$ provided 13 mg of the title compound. ^{1}H

NMR (300 MHz, $CDCl_3$) δ 7.13 (t, 1H), 6.87 (d, 2H), 5.29 (s, 2H), 4.87 (s, 2H), 4.14 (m, 6H), 3.72 (d, 2H), 3.13 (m, 1H), 1.33 (t, 6H), 1.26 (d, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 21.2.

Example X53



101



Monophenol Allylphosphonate **99c**: To a solution of allylphosphonic dichloride **99a** (4 g, 25.4 mmol) and phenol (5.2 g, 55.3 mmol) in CH_2Cl_2 (40 mL) at 0°C was added TEA (8.4 mL, 60 mmol). After stirred at room temperature for 1.5 h, the mixture was diluted with hexane-ethyl acetate and washed with HCl (0.3 N) and water. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtered through a pad of silica gel (eluted with 2:1 hexane-ethyl acetate) to afford crude product diphenol allylphosphonate **99b** (7.8 g, containing the excessive phenol) as an oil which was used directly without any further purification. The crude material was dissolved in CH_3CN (60 mL), and NaOH (4.4N, 15 mL) was added at 0°C. The resulted mixture was stirred at room temperature for 3 h, then neutralized with acetic acid to pH = 8 and concentrated under reduced pressure to remove most of the acetonitrile. The residue was dissolved in water (50 mL) and washed with CH_2Cl_2 (3X25 mL). The aqueous phase was acidified with concentrated HCl at 0°C and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, evaporated and co-evaporated with toluene under reduced pressure to yield desired monophenol allylphosphonate **99c** (4.75 g. 95%) as an oil.

Monolactate Allylphosphonate **99e**: A solution of monophenol allylphosphonate **99c** (4.75 g, 24 mmol) in toluene (30 mL) was treated with $SOCl_2$ (5 mL, 68 mmol) and DMF (0.05 mL). After stirred at 65°C for 4 h, the reaction was completed as shown by ^{31}P NMR. The reaction mixture was evaporated and co-evaporated with toluene under reduced pressure to give mono chloride **99d** (5.5 g) as an oil. A solution of chloride **99d** in CH_2Cl_2 (25 mL) at 0°C was added ethyl (s)-lactate (3.3 mL, 28.8 mmol), followed by TEA. The mixture was stirred at 0°C for 5 min then at room temperature for 1 h, and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and HCl (0.2N), the organic phase was washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford desired monolactate **99e** (5.75 g, 80%) as an oil (2:1 mixture of two isomers).

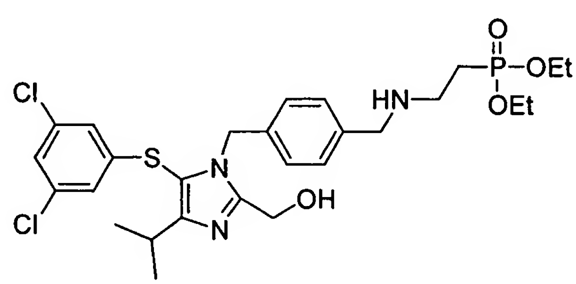
Aldehyde **99f**: A solution of allylphosphonate **99e** (2.5 g, 8.38 mmol) in CH_2Cl_2 (30 mL) was bubbled with ozone air at –78°C until the solution became blue, then bubbled with nitrogen until the blue color disappeared. Methyl sulfide (3 mL) was added at –78°C. The mixture was warmed up to room temperature, stirred for 16 h and concentrated under reduced pressure to give desired aldehyde **99f** (3.2 g, as a 1:1 mixture of DMSO).

Compound **98** was prepared from compound **29** following the sequence of steps described in Example X19. Compound **99** was prepared from compound **96** following the sequence of steps described in Example X51 and X52, except for substituting 4-nitro benzyl bromide for compound **95**.

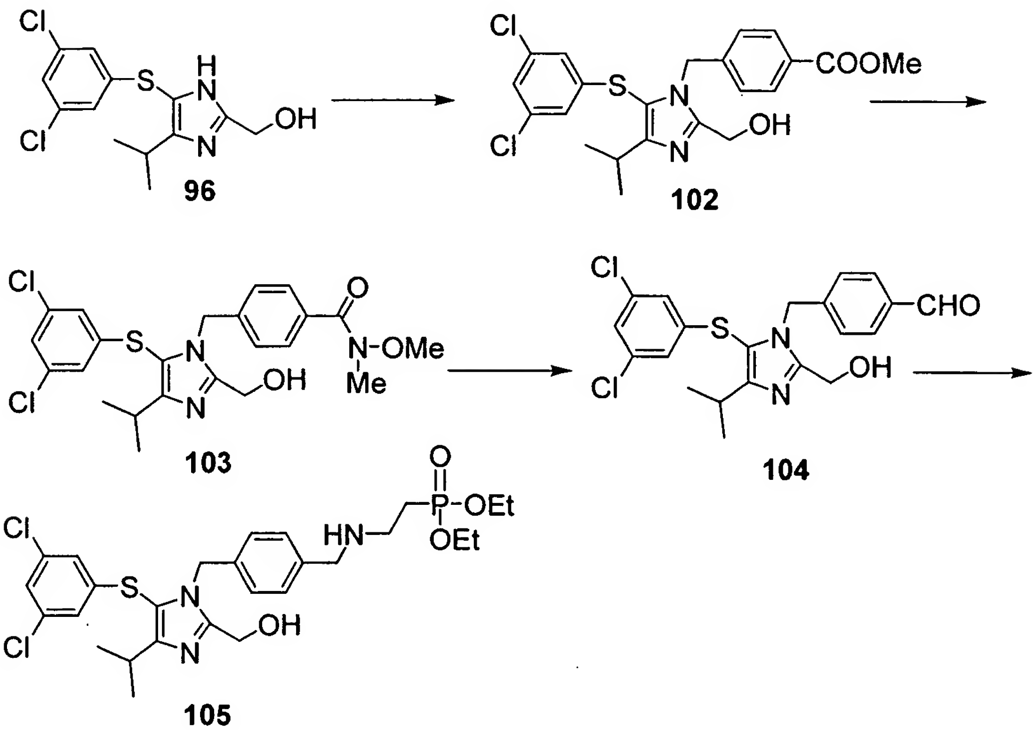
Aniline **100**: To a solution of compound **99** (100 mg, 0.202 mmol) in EtOH (2 mL) was added acetic acid (2 mL) and zinc dust (40 mg, 0.606 mmol). After the reaction mixture was stirred for 30 min at room temperature, the mixture was concentrated under reduced pressure. The crude product was purified on silica gel (eluting 5-6% $MeOH/CH_2Cl_2$) to give aniline **100** (43 mg, 41%) as a yellow oil.

Title compound phosphonate **101**: To a solution of aniline **100** (22 mg, 0.042 mmol) and aldehyde **99f** (17 mg, 0.046 mmol) in MeOH (2 mL) was added acetic acid (10 μL, 0.17 mmol) and 4Å molecular sieves (10 mg). After the reaction mixture was stirred for 2 h at room temperature, $NaCNBH_3$ (5 mg, 0.084 mmol) was added. After the reaction mixture was stirred for an additional 4 h at room temperature, the mixture was concentrated under reduced pressure. The residue was partitioned between EtOAc and sat. $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified on silica gel (eluting 5-6% $MeOH/CH_2Cl_2$) to give title compound phosphonate **101** (25 mg, 79%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (dd, 2H), 7.21 (m, 3H), 7.02 (bs, 1H), 6.79 (d, 2H), 6.64 (t, 2H), 6.42 (dd, 2H), 5.21 (s, 2H), 5.10 (s, 2H), 5.02 (m, 1H), 4.75 (bs, 2H), 4.20 (m, 2H), 3.53 (m, 2H), 3.13 (m, 1H), 2.31 (m, 2H), 1.58 (d, 1.5H), 1.38 (d, 1.5H), 1.28 (d, 6H), 1.25 (t, 3H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 28.4, 26.5.

<u>Example X54</u>



105



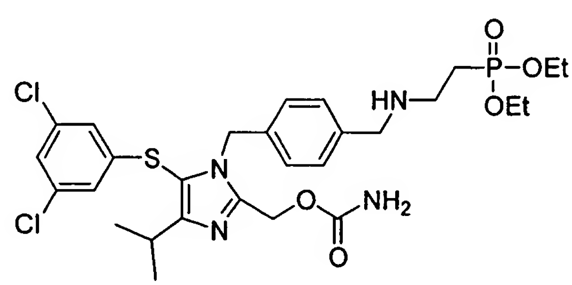
Compound **102** was prepared from compound **96** following the sequence of steps described in Example X51, except for substituting methyl 4-bromomethyl benzoate for compound **95**.

Amide **103**: A solution of ester **102** (262 mg, 0.563 mmol) in THF (5 mL) and CH_3CN (2 mL) was treated with 1N NaOH (1.13 mL, 1.13 mmol). After the reaction mixture was stirred for 2 h at 60°C, the mixture was concentrated under reduced pressure. The residue was partitioned between EtOAc and 1N HCl. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 5-10% $MeOH/CH_2Cl_2$) to give the carboxylic acid (120 mg, 47%) as a colorless oil. A solution of the above carboxylic acid (120 mg, 0.266 mmol) and N,O-dimethylhydroxylamine (29 mg, 0.293 mmol) in DMF (3 mL) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (61 mg, 0.319 mmol), 1-hydroxybenzotriazole hydrate (43 mg, 0.319 mmol), and triethylamine (55 μL, 0.399 mmol). After the reaction mixture was stirred for 18 h at room temperature, the mixture was partitioned between EtOAc and H_2O. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 3-4% $MeOH/CH_2Cl_2$) to give the amide **103** (107 mg, 81%) as a colorless oil.

Aldehyde **104**: A solution of amide **103** (106 mg, 0.214 mmol) in THF (5 mL) was treated with 1.5M DIBAL-H in toluene (0.43 mL, 0.642 mmol) at 0°C. After the reaction mixture was stirred for 1 h at 0°C, the mixture was quenched with 1M sodium potassium tartrate and stirred for an additional 3 d. The aqueous phase was extracted with EtOAc, and the organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give crude aldehyde **104** as a colorless oil.

Title compound **105**: To a solution of aldehyde **104** (91 mg, 0.21 mmol) in MeOH (5 mL) was added diethyl(aminoethyl) phosphonate (63 mg, 0.231 mmol), acetic acid (48 μL, 0.231 mmol) and 4Å molecular sieves (10 mg). After the reaction mixture was stirred for 2 h at room temperature, $NaCNBH_3$ (26 mg, 0.42 mmol) was added. After the reaction mixture was stirred for an additional 18 h at room temperature, the mixture was concentrated under reduced pressure. The residue was partitioned between EtOAc and sat. $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 5-10% $MeOH/CH_2Cl_2$) to give phosphonate **105** (10 mg, 8% over 2 steps) as a colorless oil. ^1H NMR (300 MHz, CD_3OD) δ 7.15 (d, 2H), 7.10 (t, 1H), 7.06 (d, 2H), 6.65 (t, 2H), 5.34 (s, 2H), 4.73 (s, 2H), 4.09 (m, 4H), 3.68 (s, 2H), 3.12 (m, 1H), 2.83 (m, 2H), 2.04 (m, 2H), 1.30 (t, 6H), 1.24 (d, 6H). ^{31}P NMR (300 MHz, CD_3OD) δ 30.6.

<u>Example X55</u>

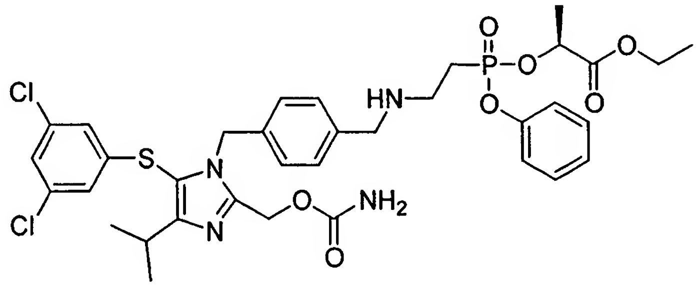


106

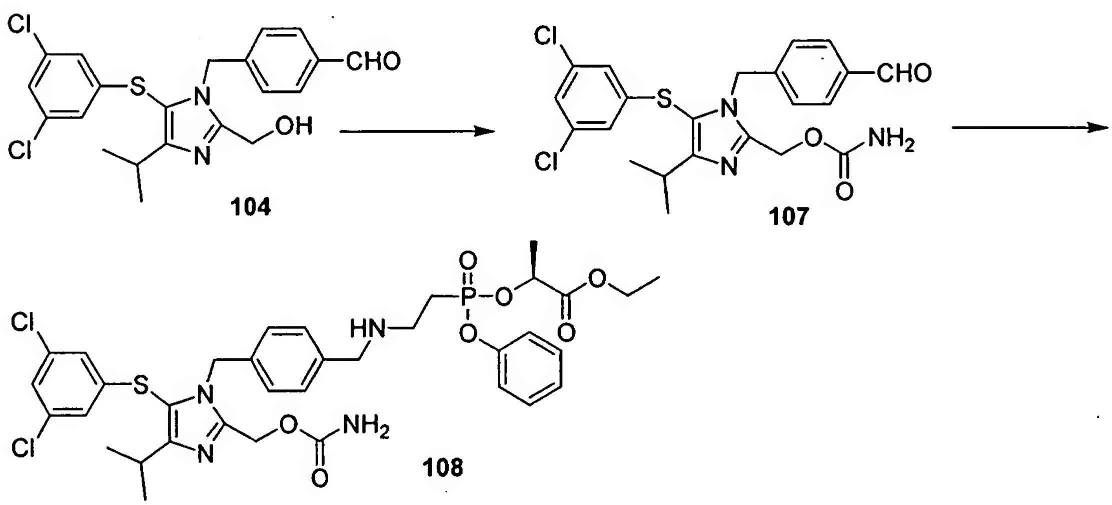
The title compound **106** was prepared following the sequence of steps described in Example X29, except for substituting compound **105** for compound **68**. Purification of the crude final product on preparative thin layer chromatography eluted with 7% $MeOH/CH_2Cl_2$ provided 6 mg of the title compound. ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, 2H), 7.02 (bs, 1H), 6.88 (d,

2H), 6.67 (t, 2H), 5.21 (s, 2H), 5.17 (s, 2H), 4.76 (bs, 2H), 4.08 (m, 4H), 3.70 (s, 2H), 3.15 (m, 1H), 2.86 (m, 2H), 1.97 (m, 2H), 1.31 (t, 6H), 1.29 (d, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 30.6.

Example X56

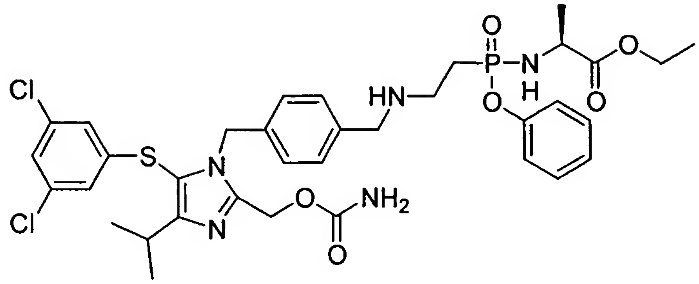


108

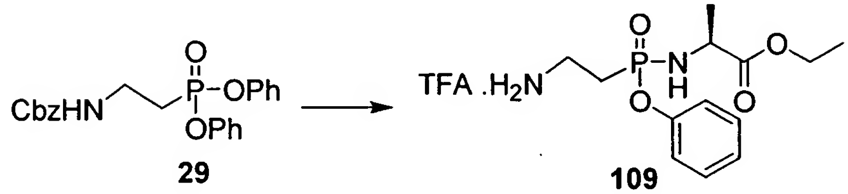


Compound **107** was prepared following the sequence of steps described in Example X29, except for substituting compound **104** for compound **68**. The title compound was prepared following the sequence of steps described in Example X55, except for substituting compound **98** for aminoethyl phosphonic acid diethyl ester. Purification of the crude final product on preparative thin layer chromatography eluted with 7% MeOH/CH_2Cl_2 provided 24 mg of the title compound **108**. ^{1}H NMR (300 MHz, $CDCl_3$) (5:1 diastereomeric ratio) δ 7.34 (t, 2H), 7.17 (m, 5H), 7.01 (t, 1H), 6.86 (d, 2H), 6.66 (t, 2H), 5.20 (bs, 4H), 4.96 (m, 1H), 4.63 (bs, 2H), 4.19 (m, 2H), 3.73 (s, 2H), 3.15 (m, 1H), 3.02 (m, 2H), 2.27 (m, 2H), 1.36 (d, 3H), 1.29 (d, 6H) 1.27 (m, 3H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 29.1, 27.4.

Example X57

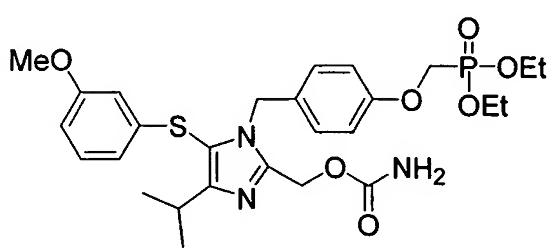


110

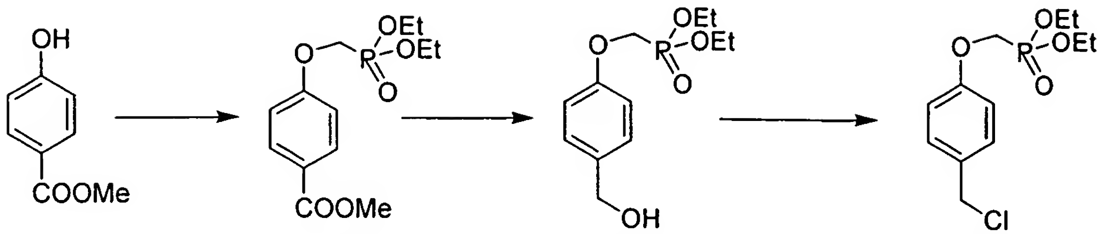


Compound **109** was prepared from compound **29** following the sequence of steps described in Example X19. The title compound was prepared following the sequence of steps described in Example X55, except for substituting compound **109** for aminoethyl phosphonic acid diethyl ester. Purification of the crude final product on silica gel eluted with 5-6% $MeOH/CH_2Cl_2$ provided 8 mg of the title compound. ^1H NMR (300 MHz, $CDCl_3$) (1.8:1 diastereomeric ratio)δ 7.31 (m, 2H), 7.16 (m, 5H), 7.01 (bs, 1H), 6.88 (d, 2H), 6.66 (bs, 2H), 5.21 (s, 2H), 5.20 (s, 2H), 4.69 (bd, 2H), 4.27 (bt, 1H), 4.12 (m, 3H), 3.75 (m, 2H), 3.16 (m, 1H), 2.99 (m, 2H), 2.11 (m, 2H), 1.30 (d, 6H), 1.22 (m, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 31.3, 30.8.

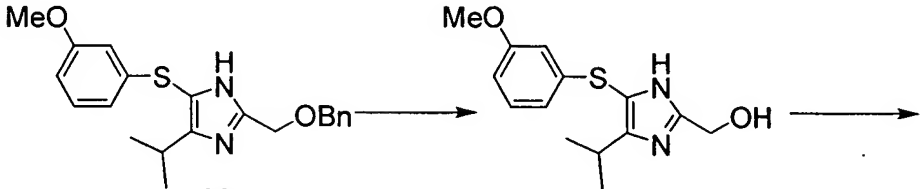
Example X58



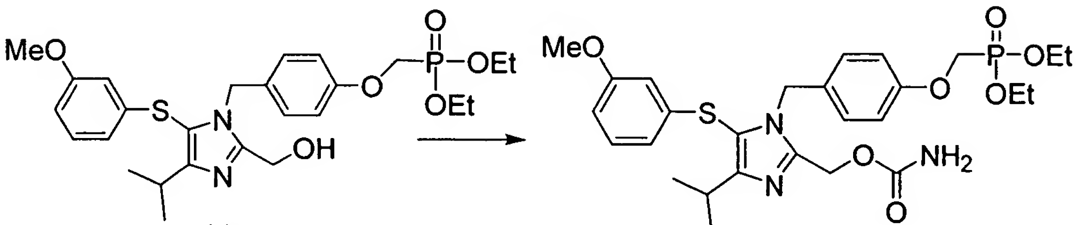
115



111 **112** **112a** **112b**



36 **113**



114 **115**

Compound **112**: A solution of methyl 4-hydroxybenzoate **111** (0.977 g, 6.42 mmol) and trifluoro-methanesulfonic acid diethoxy-phosphorylmethyl ester (2.12 g, 7.06 mmol) in THF (50 mL) was treated with Cs_2CO_3 (4.18 g, 12.84 mmol). The resulting reaction mixture was stirred for 1 h at room temperature before it was partitioned between EtOAc and sat. aqueous NH_4Cl and extracted with EtOAc (3x). The organic phase was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. Purification of the crude product on silica gel (eluted with 60-90% EtOAc/hexane) provided 1.94 g (quantitative) of methyl phosphonobenzoate compound **112** as a clear oil.

Alcohol **112a**: A solution of **112** (1.94 g, 6.42 mmol) in Et_2O (40 mL) was treated with $LiBH_4$ (0.699 g, 32.1 mmol) and THF (10 mL). After the reaction mixture was stirred for 12 h at room temperature, the mixture was quenched with water and extracted with EtOAc (3x). The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified on silica gel (eluted with 2-5% $MeOH/CH_2Cl_2$) to give 1.48 g (84%) of alcohol compound **112a** as a colorless oil.

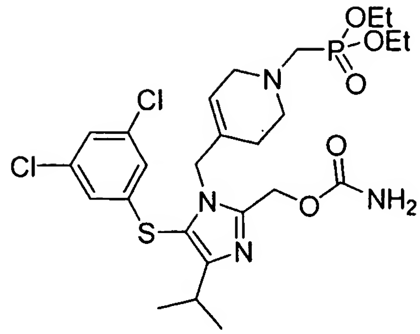
Chloride **112b**: A solution of **112a** (315 mg, 1.15 mmol) in MeCN (6 mL) was treated with methanesulfonyl chloride (97.6 μL, 1.26 mmol), TEA (175 μL, 1.26 mmol), LiCl (74.5 mg, 1.72 mmol). After stirring at room temperature for 30 min., the mixture was concentrated under reduced pressure, partitioned between EtOAc and sat. $NaHCO_3$, and extracted with EtOAc (3x). The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. Purification of the crude product on silica gel (eluted with 2-4% $MeOH/CH_2Cl_2$) provided 287 mg (85%) of chloride compound **112b** as a clear pale yellow oil.

Alcohol compound **113**: A solution of benzyl ether **36** (120 mg, 0.326 mmol) in EtOH (2 mL) was treated with conc. HCl (2 mL). After the reaction mixture was refluxed at 100°C for 1 day, the mixture was concentrated under reduced pressure, partitioned between EtOAc and sat. $NaHCO_3$, and extracted with EtOAc (3x). The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure to provide the crude alcohol compound **113** (90 mg, 99%) as a white solid.

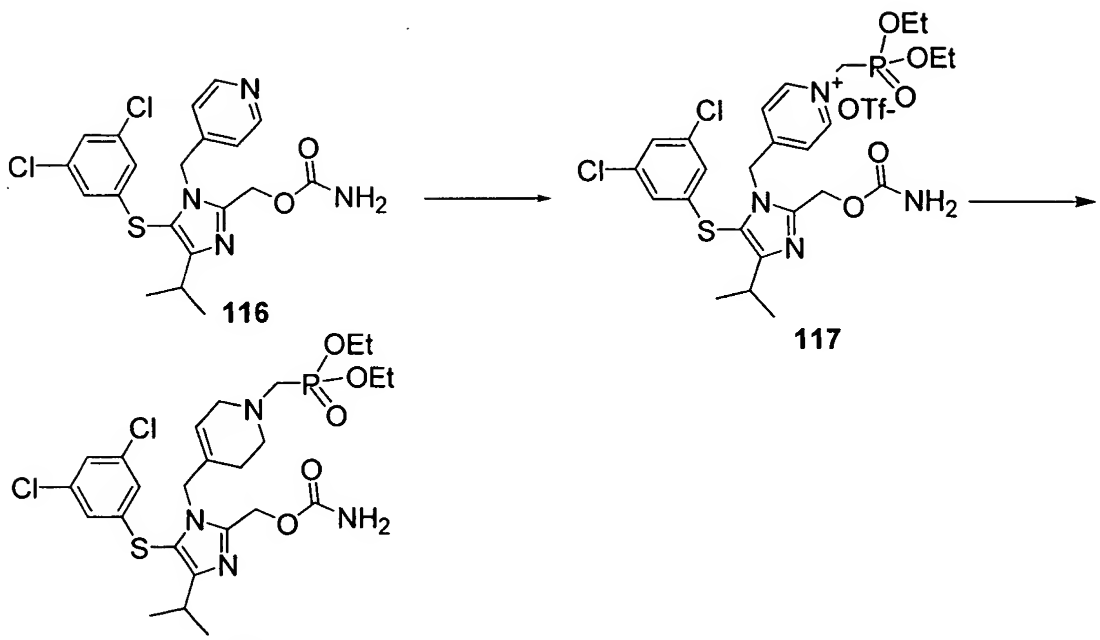
Compound **114**: A solution of alcohol compound **113** (16.8 mg, 0.060 mmol) and chloride compound **112b** (21.1 mg, 0.072 mmol) in THF (1.5 mL) was treated with powder NaOH (3.5 mg, 0.090 mmol), lithium iodide (12.0 mg, 0.090 mmol), and tetrabutylammonium bromide (9.70 mg, 0.030 mmol). After the reaction mixture was stirred at room temperature for 15 h, the mixture was partitioned between EtOAc and sat. NH_4Cl. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified on silica gel (eluted with 3-6% $MeOH/CH_2Cl_2$) to give compound **114** (19.7 mg, 61%) as a colorless oil.

Title compound **115**: A solution of **114** (19.7 mg, 0.037 mmol) in CH_2Cl_2 (1 mL) was treated with trichloroacetyl isocyanate (13.2 μL, 0.111 mmol). After the reaction mixture was stirred at room temperature for 20 min, 2 mL of CH_2Cl_2 (saturated with NH_3) was added to the mixture. After stirring at room temperature for 1 h, the mixture was bubbled with N_2 for 1 h. The mixture was then concentrated under reduced pressure and purified on silica gel (eluted with 4-6% $MeOH/CH_2Cl_2$) to give the titled compound **115** (18.5 mg, 87%) as a clear oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.09 (t, 1H), 6.90 (d, 2H), 6.78 (d, 2H), 6.63 (dd, 1H), 6.51 (dd, 1H), 6.40 (t, 1H), 5.15 (s, 2H), 5.11 (s, 2H), 4.70 (b, 2H), 4.21 (m, 6H), 3.70 (s, 3H), 3.22 (m, 1H), 1.36 (t, 6H), 1.29 (d, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 19.2.

Example X59



118

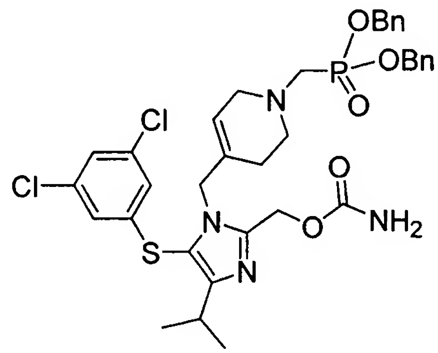


116 **117** **118**

A suspension of compound **116** (15mg, 0.03mmol) in acetone d-6 was treated with trifluoro-methanesulfonic acid diethoxy-phosphorylmethyl ester (12mg, 0.04 mmol). The solution was stirred overnight at ambient temperature. Concentration afforded compound **117**. Compound **117** (22mg, 0.03mmol) was suspended in EtOH (2mL) and an excess of sodium borohydride(15mg, 0.39mmol) was added. The solution was stirred at room temperature. After 30 minutes, sodium borohydride (15mg, 0.39mmol) was added again. Acetic acid (1ml) in EtOH was added 2 hours later followed by the addition of sodium borohydride (15mg, 0.39mmol). After 30 minutes, the solution was concentrated. The residue was dissolved in saturated aqueous $NaHCO_3$ and extracted with EtOAc (x3). The organic layers were washed

with brine and dried over $MgSO_4$. The solution was filtered, concentrated and purified using a TLC plate (5% CH_3OH/CH_2Cl_2) to give 14 mg (80%) of the desired product. ^{1}H NMR ($CDCl_3$, 500mHz): 7.13 (s, 1H), 6.83 (s, 2H), 5.16 (s, 2H), 5.01 (s, 1H), 4.51 (s, 2H), 4.14 (m, 4H), 3.15 (m, 1H), 3.00 (s, 2H), 2.80 (d, 2H), 2.68 (t, 2H), 1.97 (s, 2H), 1.33 (t, 6H), 1.29 (d, 6H).

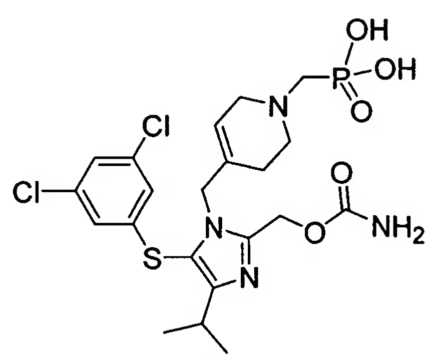
Example X60



119

Title compound **119** was prepared following the sequence of steps described in Example X59 by substituting trifluoro-methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester for trifluoro-methanesulfonic acid diethoxy-phosphorylmethyl ester. Purification of the crude final product on silica gel eluted with (2.5% - 5% CH_3OH/CH_2Cl_2) provided 71 mg (65%) of the title compound. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.35 (s, 10H), 7.11 (s,1H) 6.82 (s, 2H), 5.16 (s, 2H), 5.04 (d, 4H), 4.99 (s, 1H), 4.49 (s, 2H), 3.15 (m, 1H), 2.96 (s, 2H), 2.81 (d, 2H), 2.63 (t, 2H), 1.91 (s, 2H), 1.29ppm(d, 6H).

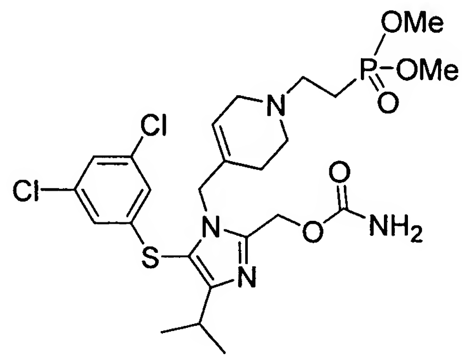
Example X61



120

Compound **119** was stirred in 4M HCl/dioxane overnight at ambient temperature. The mixture was concentrated and purified using HPLC (20% CH_3CN/H_2O) to provide 20 mg of the title compound **120**. ^{1}H NMR (CD_3OD_3, 500 MHz) 7.33 (s,1H) 7.00 (s, 2H), 5.22 (s, 2H), 5.12 (s, 1H), 4.79 (s, 2H), 3.80 (s, 2H), 3.49 (s, 2H), 3.23 (m, 2H), 3.21 (m, 1H), 2.40 (s, 2H), 1.28 (d, 6H).

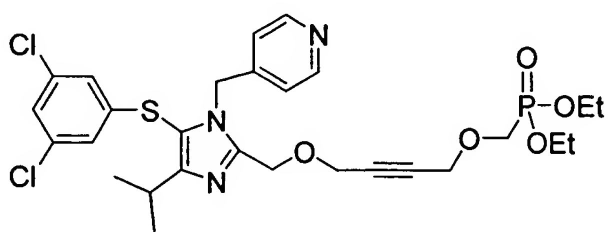
Example X62



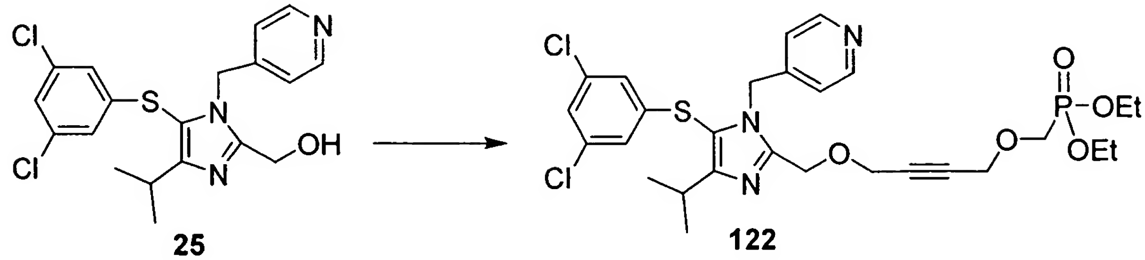
121

Compound 121 was prepared following the sequence of steps described in Example X59 by substituting trifluoro-methanesulfonic acid dimethoxy-phosphorylethyl ester for trifluoro-methanesulfonic acid diethoxy-phosphorylmethyl ester. Purification of the crude final product on TLC plate eluted with (5% CH_3OH/CH_2Cl_2) provided 11 mg (65%) of the title compound. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.34 (d, 2H). 7.20 (d, 2H), 7.19 (d,1H) 7.13 (s, 1H), 6.83 (s, 2H), 5.18 (s, 2H), 5.03 (s, 1H), 4.98 (m, 1H), 4.52 (s, 2H), 4.22 (m, 2H), 3.15 (m, 1H), 2.91 (s, 2H), 2.81 (s, 2H), 2.54 (s, 2H), 2.29 (m, 2H), 2.01 (d, 2H), 1.56 (d, 3H), 1.38 (d,3H), 1.28 (q, 3H), 1.28 (d, 6H).

Example X63



122



A solution of **25** (33.2 mg, 0.081 mmol) in DMF (3 mL) under N_2 at 0°C was treated with NaH. After stirring at 0°C for 10 min, **95** (23 mg, 0.077 mmol) was added, and the resulting mixture was slowly raised to room temperature and stirred at room temperature for 8 h. The mixture was then poured into water, and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The crude product was purified on TLC plate (eluted with 3% MeOH/CH_2Cl_2) to provide 17.9 mg of the title compound **122**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, 2H), 7.04 (t, 1H), 6.88 (d, 2H), 6.67 (d, 2H), 5.24 (s, 2H), 4.67 (s, 2H), 5.02 (m, 1H), 4.27 (bs, 2H), 4.22 (bs, 2H), 4.19 (m, 4H), 3.82 (m, 2H), 3.16 (m, 1H), 1.35 (t, 6H), 1.30 (d, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 20.8.

<u>Example X64: Anti-HIV-1 Cell Culture Assay</u>

The assay is based on quantification of the HIV-1-associated cytopathic effect by a colorimetric detection of the viability of virus-infected cells in the presence or absence of tested inhibitors. The HIV-1-induced cell death is determined using a metabolic substrate 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT) which is converted only by intact cells into a product with specific absorption characteristics as described by Weislow OS, Kiser R, Fine DL, Bader J, Shoemaker RH and Boyd MR (1989) *J Natl Cancer Inst* 81, 577.

<u>Assay protocol for determination of EC50</u>:

1. Maintain MT2 cells in RPMI-1640 medium supplemented with 5% fetal bovine serum and antibiotics.
2. Infect the cells with the wild-type HIV-1 strain IIIB (Advanced Biotechnologies, Columbia, MD) for 3 hours at 37°C using the virus inoculum corresponding to a multiplicity of infection equal to 0.01.

3. Distribute the infected cells into a 96-well plate (20,000 cells in 100 μL/well) and add various concentrations of the tested inhibitor in triplicate (100 μL/well in culture media). Include untreated infected and untreated mock-infected control cells.
4. Incubate the cells for 5 days at 37°C.
5. Prepare XTT solution (6 ml per assay plate) at a concentration of 2mg/mL in a phosphate-buffered saline pH 7.4. Heat the solution in water-bath for 5 min at 55°C. Add 50 μL of N-methylphenazonium methasulfate (5 μg/mL) per 6 mL of XTT solution.
6. Remove 100 μL media from each well on the assay plate.
7. Add 100 μL of the XTT substrate solution per well and incubate at 37°C for 45 to 60 min in a CO_2 incubator.
8. Add 20 μL of 2% Triton X-100 per well to inactivate the virus.
9. Read the absorbance at 450 nm with subtracting off the background absorbance at 650 nm.
10. Plot the percentage absorbance relative to untreated control and estimate the EC50 value as drug concentration resulting in a 50% protection of the infected cells.

Example X65: Cytotoxicity Cell Culture Assay (Determination of CC50):

The assay is based on the evaluation of cytotoxic effect of tested compounds using a metabolic substrate 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT) as described by Weislow OS, Kiser R, Fine DL, Bader J, Shoemaker RH and Boyd MR (1989) *J Natl Cancer Ins* 81, 577.

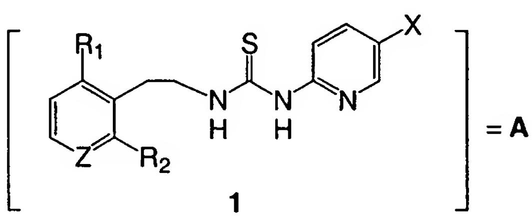
Assay protocol for determination of CC50:

1. Maintain MT-2 cells in RPMI-1640 medium supplemented with 5% fetal bovine serum and antibiotics.
2. Distribute the cells into a 96-well plate (20,000 cell in 100 μL media per well) and add various concentrations of the tested compound in triplicate (100 μL/well). Include untreated control.
3. Incubate the cells for 5 days at 37°C.
4. Prepare XTT solution (6 ml per assay plate) in dark at a concentration of 2mg/mL in a phosphate-buffered saline pH 7.4. Heat the solution in a water-bath at 55°C for 5 min. Add 50 μL of N-methylphenazonium methasulfate (5 μg/mL) per 6 mL of XTT solution.

5. Remove 100 μL media from each well on the assay plate and add 100 μL of the XTT substrate solution per well. Incubate at 37°C for 45 to 60 min in a CO_2 incubator.
6. Add 20 μL of 2% Triton X-100 per well to stop the metabolic conversion of XTT.
7. Read the absorbance at 450 nm with subtracting off the background at 650 nm.
8. Plot the percentage absorbance relative to untreated control and estimate the CC50 value as drug concentration resulting in a 50% inhibition of the cell growth. Consider the absorbance being directly proportional to the cell growth.

PETT-like phosphonate NNRTI compounds

The PETT class of compound has demonstrated activity in inhibiting HIV replication. The present invention provides novel analogs of PETT class of compound. Such novel PETT analogs possess all the utilities of PETT and optionally provide cellular accumulation as set forth below.



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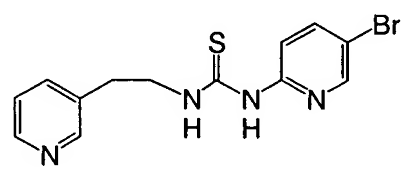
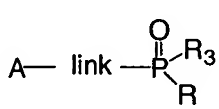
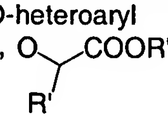


trovirdine

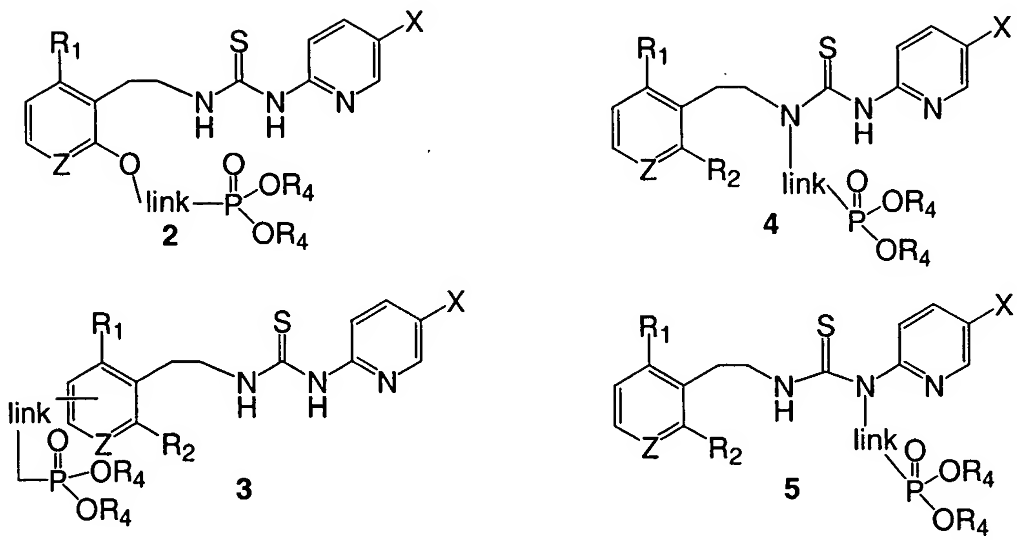
R_1 = H, F, Cl, OMe   Z = CH
R_2 = H, F, Cl, OMe   Z = N when R_1 and R_2 are H
X = Cl, Br, CN



link = linkage group
R = OAr, O-heteroaryl, amino acid ester
substituted OAr, O-heteroaryl
R_3 = amino acid ester, 

PETT Illustration 1

The intermediate phosphonate esters required for conversion into the prodrug phosphonate moieties bearing amino acid, or lactate esters are shown in PETT Illustration 2.

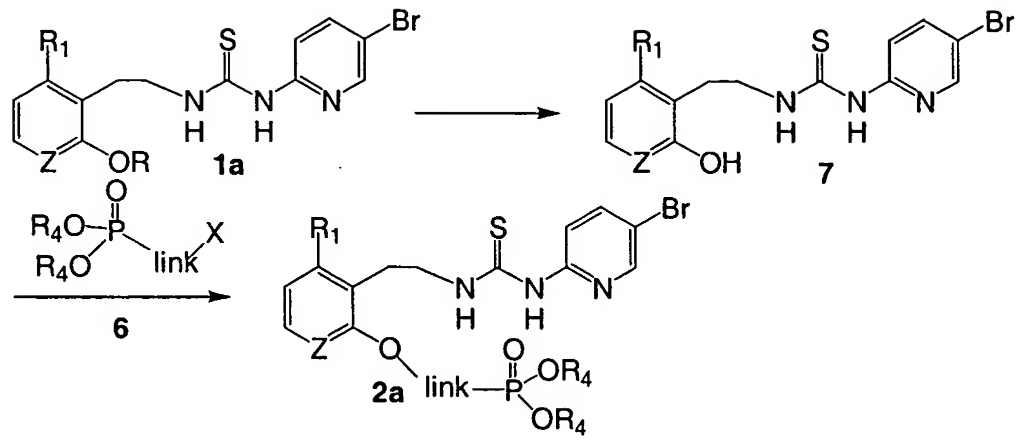


PETT Illustration 2

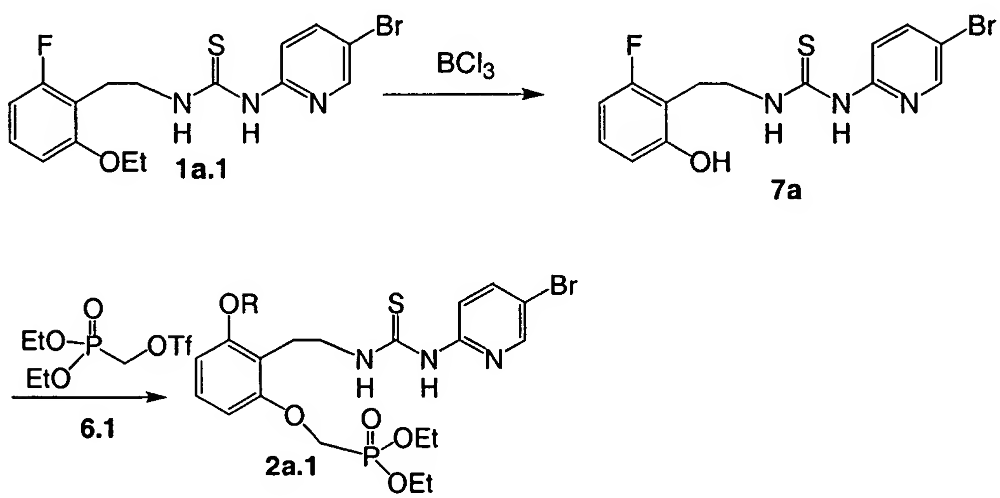
PETT **1** compounds, analogs of trovirdine, are obtained following the procedures described in WO/9303022 and *J. Med. Chem.* **1995**, *38*, 4929-4936 and **1996**, *39*,4261-4274. Preparation of PETT-like phosphonate NNRTI compounds, *e.g.*, phosphonate analog type **2** is outlined in PETT Scheme 1. PETT analog **1a** is obtained following the above mentioned literature procedure. Alkyl group of **1a** is then removed using such as, for example BCl_3 to give phenol **7**, many examples are described in Greene and Wuts, Protecting Groups in Organic Synthesis, 3rd Edition, John Wiley and Sons Inc. Conversion of **7** to the desired phosphonate analogs is realized by treatment of **7** with the phosphonate reagent **6** under suitable conditions.

For example (PETT Example 1), PETT **1a** is treated with BCl_3 to give phenol **7**. Treatment of **7** with phosphonate **6.1** in the presence of base, for example, Cs_2CO_3, affords the phosphonate **2a.1**. Using the above procedure but employing a different phosphonate reagent **5** in place of **6.1**, corresponding products **2** with different linking groups are obtained.

PETT Scheme 1



PETT Example 1

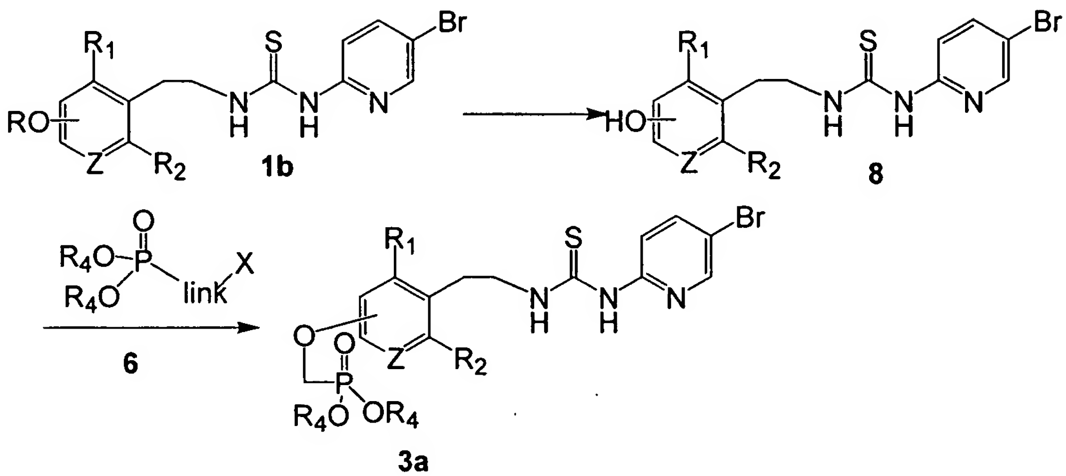


PETT Scheme 2 shows the preparation of phosphonate type 3 in PETT Illustration 2. PETT **1b** is obtained as described in WO/9303022 and *J. Med. Chem.* **1995**, *38*, 4929-4936 and **1996**, *39*,4261-4274. Alkyl group of **1b** is then removed using such as, for example BCl_3 to give phenol **8**, many examples are described in Greene and Wuts, Protecting Groups in Organic Synthesis, 3rd Edition, John Wiley and Sons Inc. Conversion of **8** to the desired phosphonate analogs is realized by treatment of **8** with the phosphonate reagent **6** under suitable conditions.

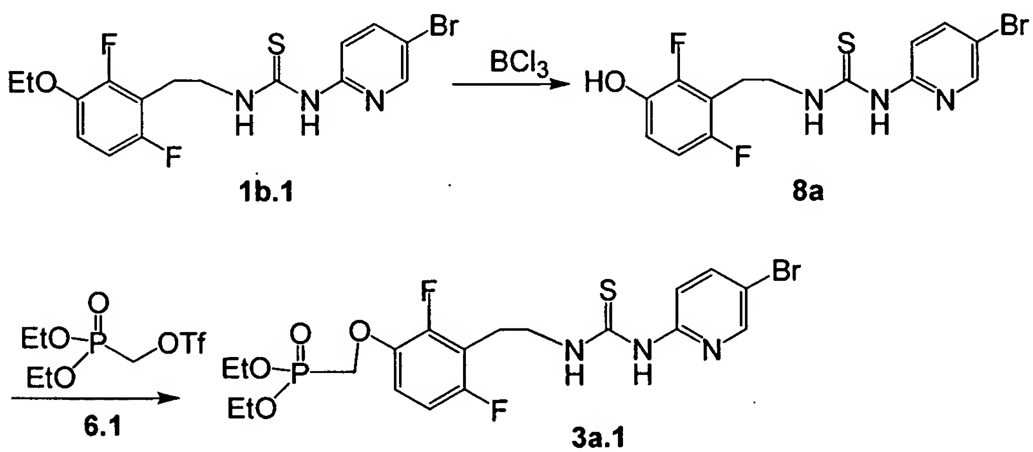
For example (PETT Example 1), PETT **1a** is treated with BCl_3 to give phenol **7**. Treatment of **7** with triflate methyl phosphonic acid diethyl ester **6.1** in the presence of base, for example, Cs_2CO_3, affords the phosphonate **2a.1**. Using the above procedure but employing a

different phosphonate reagent **6** in place of **6.1**, corresponding products **3** with different linking groups are obtained.

PETT Scheme 2



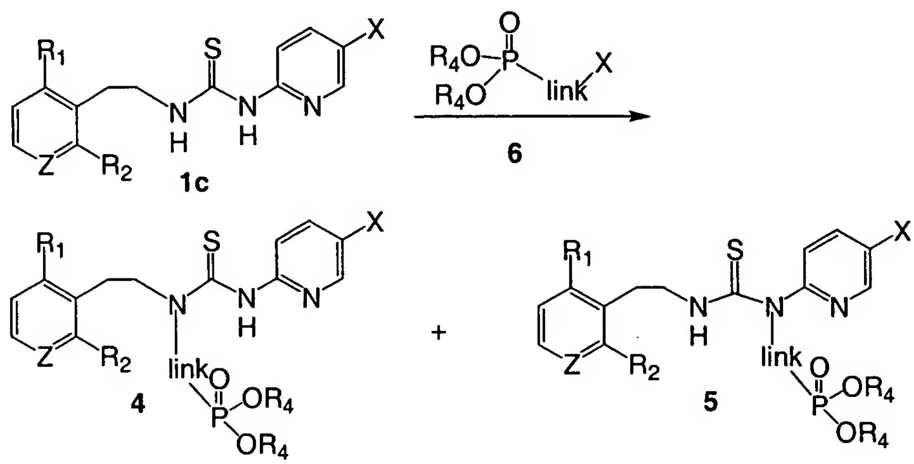
PETT Example 2



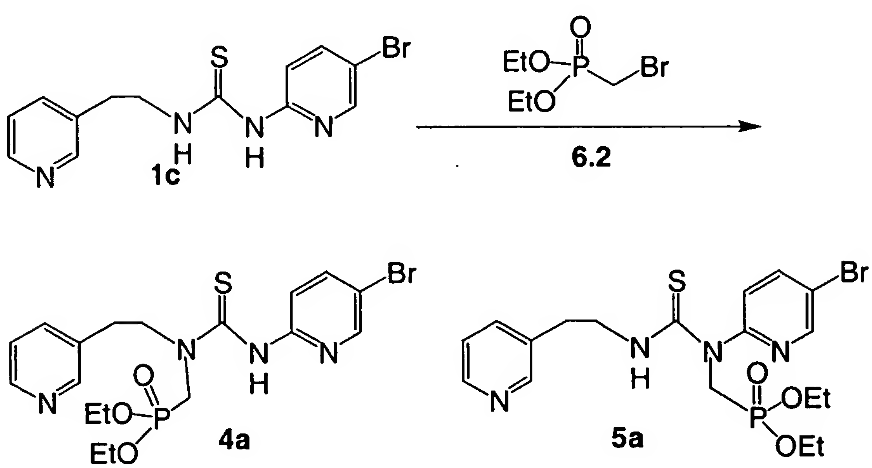
PETT Scheme 3 shows the preparation of the phosphonate linkage of type **4** and **5** to PETT. PETT **1c** is first treated with a suitable base to remove the thiourea proton, the product is then treated with 1 equivalent of a phosphonate reagent **5** bearing a leaving group such as, for example, bromine, mesyl, tosyl etc to give the alkylated product **4** and **5**. The phosphonates **4** and **5** are separated by chromatography. For example (PETT Example 3), PETT **1**, in DMF, is treated with sodium hydride followed by one equivalent of bromomethyl phosphonic acid dibenzyl ester **6.2** to give phosphonate **4a** and **5a**. Phosphonate product **4a** and **5a** are then

separated by chromatography to give pure **4a** and **5a**, respectively. Using the above procedure but employing a different phosphonate reagent **5** in place of **6.2**, corresponding products **4** and **5** with different linking groups are obtained.

PETT Scheme 3

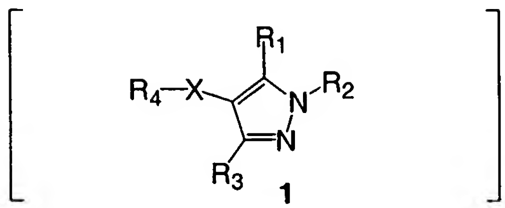


PETT Example 3



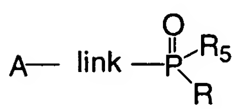
Pyrazole-like phosphonate NNRTI compounds

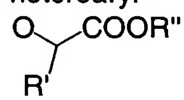
The present invention includes pyrazole-like phosphonate NNRTI compounds and describes methods for their preparation. Pyrazole-like phosphonate NNRTI compounds are potential anti-HIV agents.



= A

R_1, R_2, R_3 and R_4, X are defined as described in Patent WO02/04424.



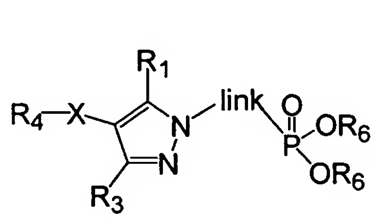
link = linkage group
R = OAr, O-heteroaryl, amino acid ester
substituted OAr, O-heteroaryl
R_5 = amino acid ester, 

Pyrazole Illustration 1

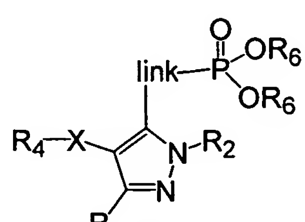
A link group includes a portion of the structure that links two substructures, one of which is pyrazole class of HIV inhibiting agents having the general formula shown above, the other is a phosphonate group bearing the appropriate R and R_5 groups. The link has at least one uninterrupted chain of atoms other than hydrogen.

Pyrazole class of compounds has shown to be inhibitors of HIV RT. The present invention provides novel analogs of pyrazole class of compound. Such novel pyrazole analogs possess all the utilities of pyrazoles and optionally provide cellular accumulation as set forth below.

The intermediate phosphonate esters required for conversion into the prodrug phosphonate moieties bearing amino acid, or lactate esters are shown in Pyrazole Illustration 2, where R_1, R_2, R_3, R_4 and X are as described in WO02/04424.



2



3

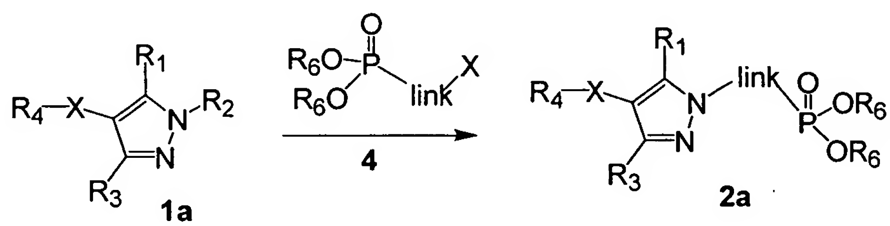
Pyrazole Illustration 2

Pyrazole **1** is obtained following the procedures described in WO02/04424.

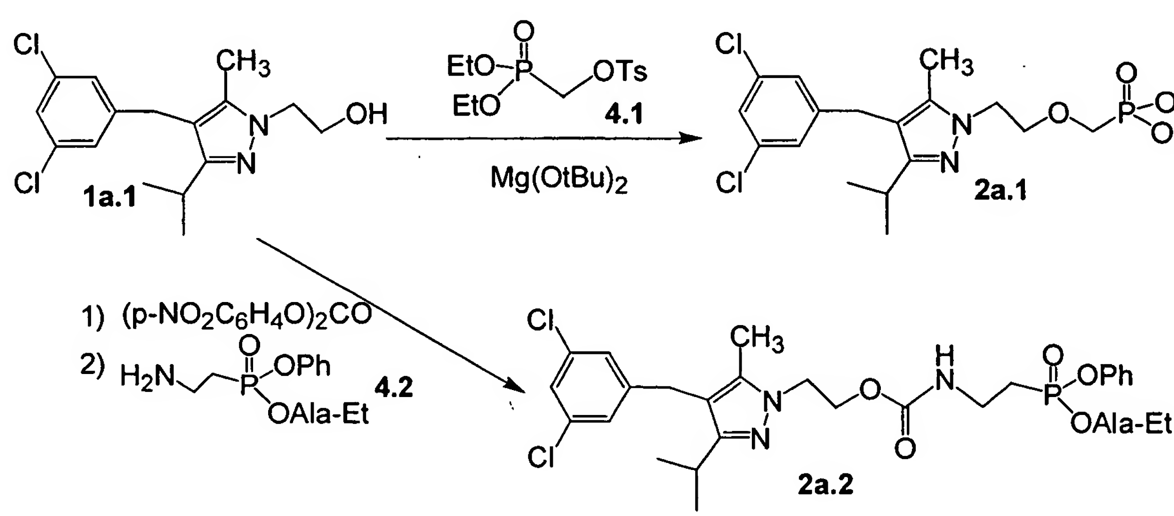
Preparation of phosphonate analog type **2** is outlined in Pyrazole Scheme 1. Pyrazole analog **1a**, which R_2 bears a function group can be used as attaching site for phosphonate prodrug, is obtained as described in the above mentioned literature. Conversion of **1a** to the desired phosphonate analogs is realized by treatment of **2a** with the phosphonate reagent **4** under suitable conditions.

For example (Pyrazole Example 1), treatment of pyrazole **1a.1** with phosphonate **4.1** in the presence of base, for example, $Mg(OtBu)_2$, affords the phosphonate **2a.1**. Using the above procedure but employing a different phosphonate reagent **4** in place of **4.1**, corresponding products **2a** with different linking groups are obtained. Alternatively, activation of the hydroxyl group with bis(4-nitrophenyl) carbonate, following by treatment with amino ethyl phosphonate **4.2** provides phosphonate **2a.2**. Using different phosphonate **4** in place of **4.2** and/or different methods for linking them together affords **2** with different linker.

Pyrazole Scheme 1

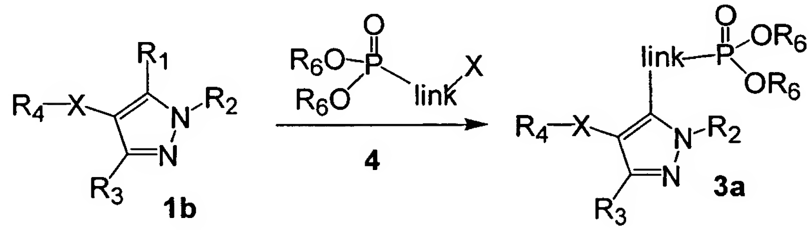


Pyrazole Example 1

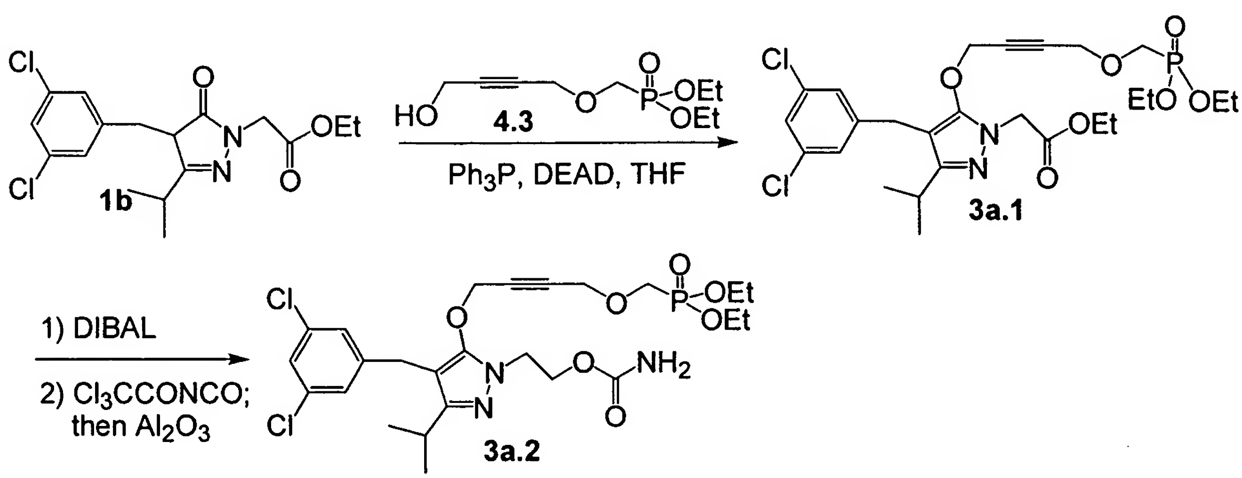


Pyrazole Scheme 2 shows the preparation of phosphonate type **3** conjugate to pyrazole in Pyrazole Illustration 2. Pyrazole **1b**, bearing a functional group at position R_1 can be used as attaching site for phosphonate prodrug, is obtained as described in WO02/04424. Conversion of **1b** to the desired phosphonate **3** analogs is realized by treatment of **1b** with the phosphonate reagent **4** under suitable conditions. For example (Pyrazole Example 2), pyrazole **1b** reacts with phosphonate **4.3** in the presence of triphenyl phosphine and DEAD in THF, affords the phosphonate **3a.1**. Phosphonate **3a.2** is obtained by first reducing the ester to alcohol, and then by treating the resulting alcohol with trichloroacetyl isocyanate, and followed by alumina. Using the above procedure but employing a different phosphonate reagent **4** in place of **4.3**, corresponding products **3** with different linking groups are obtained.

Pyrazole Scheme 2



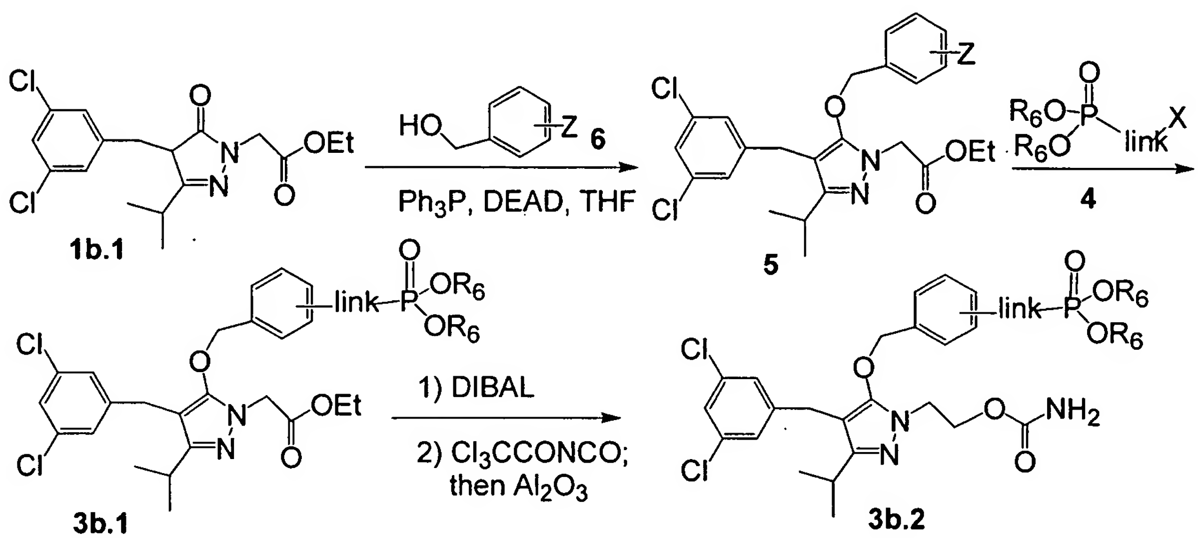
Pyrazole Example 2

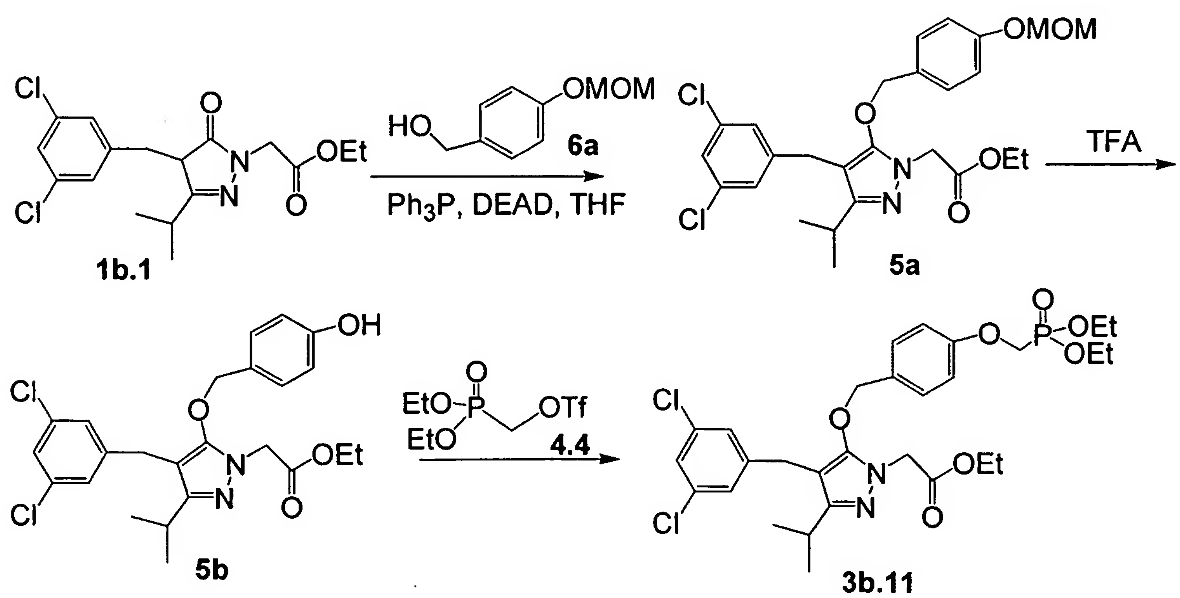


Alternatively, as shown in Pyrazole Example 3, reaction of pyrazolone **1b.1** with a moiety bearing a protected function group which can be used to attach phosphonate, for example benzyl alcohol with a protected hydroxyl or amino group, under Mitsunobu condition affords

compound **5**. The protecting group of Z is then removed, and the resulting product is reacted with phosphonate reagent yields phosphonate **3b.1**. Phosphonate **3b.1** is converted to phosphonate **3b.2** following the procedures described Example 2. Reaction of pyrazolone 1b.1with benzyl alcohol **6b** with Ph_3P/DEAD produces **5a**. The protecting group MOM- is then removed with TFA to give phenol **5b**. Treatment of phenol with triflate methyl phosphonic acid dibenzyl ester **4a** to give phosphonate **3b.11**, which is also converted to **3b.2** type of compound.

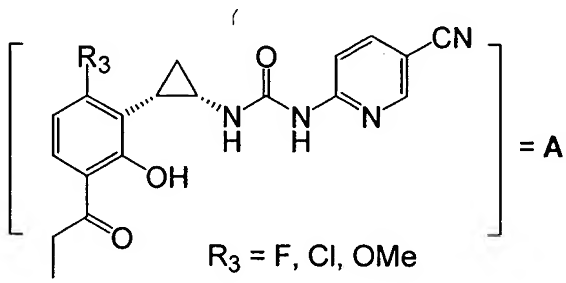
Pyrazole Example 3



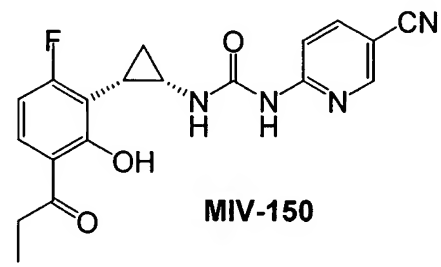


__Urea-PETT-like phosphonate NNRTI compounds__

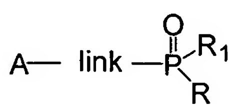
The present invention include describes Urea-PETT-like phosphonate NNRTI compounds and methods for their preparation. Urea-PETT-like phosphonate NNRTI compounds are potential anti-HIV agents.



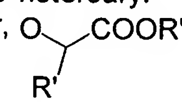
1



MIV-150



link = linkage group
R = OAr, O-heteroaryl, amino acid ester
substituted OAr, O-heteroaryl
R_1 = amino acid ester,

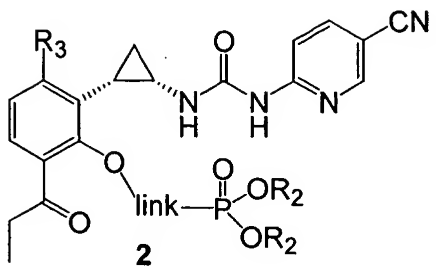


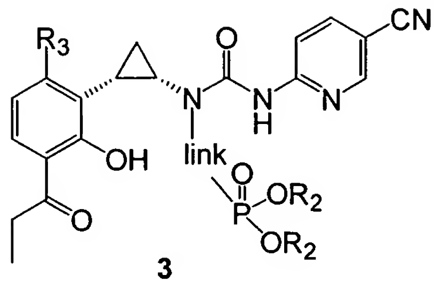
Urea-PETT Illustration 1

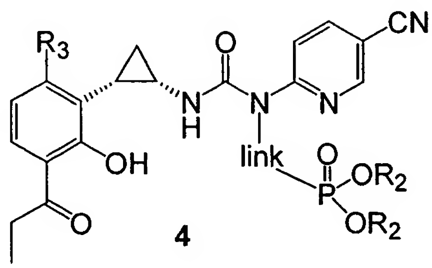
A link group includes a portion of the structure that links two substructures, one of which is Urea-PETT class of HIV inhibiting agents having the general formula shown above, the other is a phosphonate group bearing the appropriate R and R1 groups. The link has at least one uninterrupted chain of atoms other than hydrogen.

Urea-PETT class of compound has demonstrated activity in inhibiting HIV replication. The present invention provides novel analogs of urea-PETT class of compound. Such novel Urea-PETT analogs possess all the utilities of urea-PETT and optionally provide cellular accumulation as set forth below.

The intermediate phosphonate esters required for conversion into the prodrug phosphonate moieties bearing amino acid, or lactate esters are shown in Urea-PETT Illustration 2.



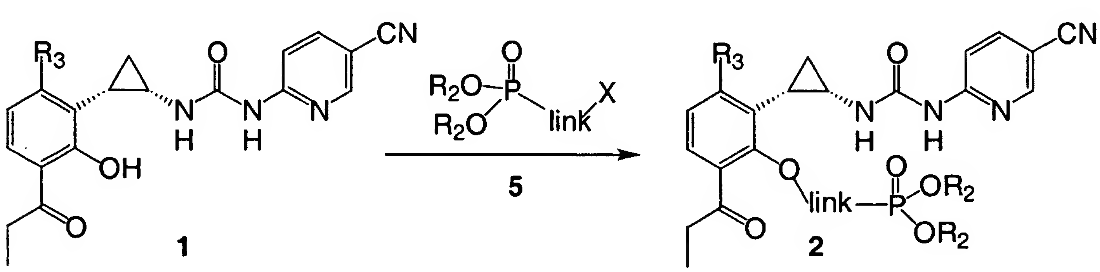




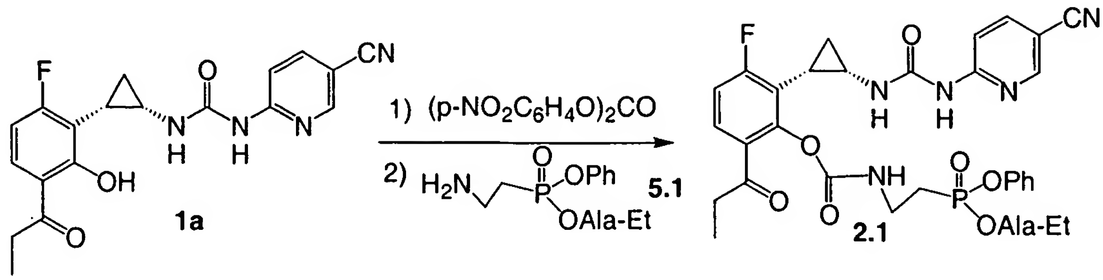
Urea-PETT Illustration 2

Preparation of phosphonate analog type **2** is outlined in Urea-PETT Scheme 1. Urea-PETT **1** is described in US Patent No. 6486183 and *J. Med. Chem.* **1999**, *42*, 4150-4160. Conversion of **1** to the desired phosphonate analogs is realized by treatment of **1** with the phosphonate reagent **5** under suitable conditions. For example (Urea-PETT Example 1), urea-PETT **1a** is activated as it *p*-nitro-phenol carbonate by reacting with bis(4-nitrophenyl)carbonate. Reaction of the resulting carbonate with amino ethyl phosphonate **5.1** in the presence of base, for example, Hunig's base, affords the phosphonate **2.1**.

Urea-PETT Scheme 1

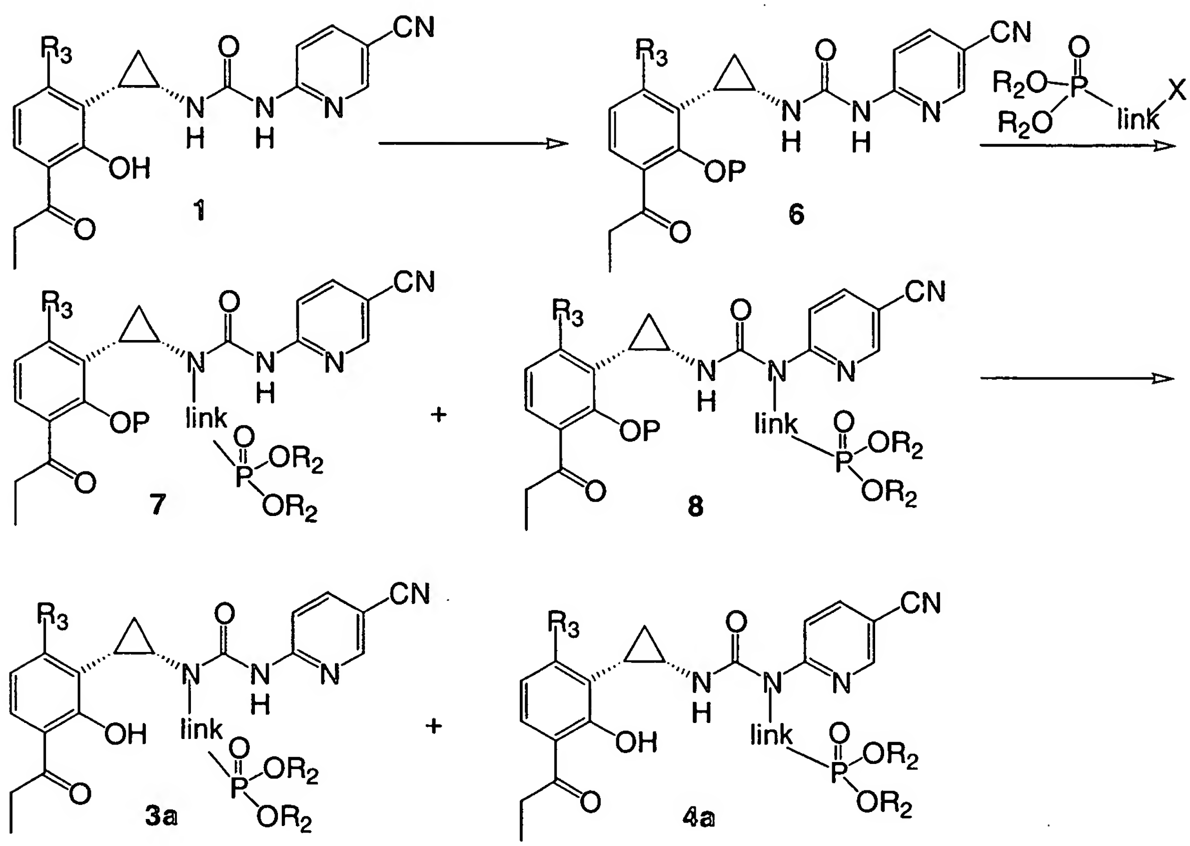


Urea-PETT Example 1

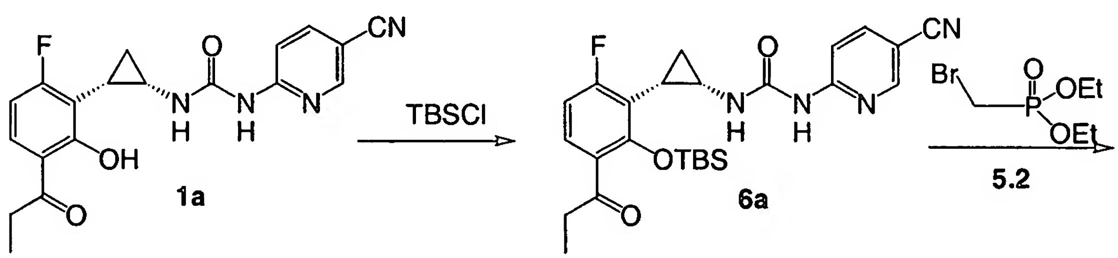


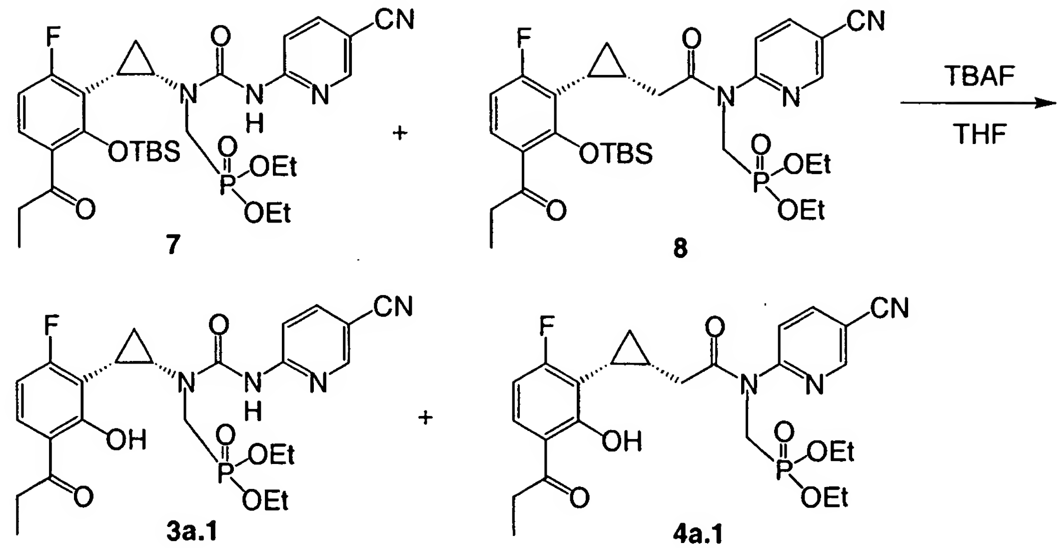
Urea-PETT Scheme 2 shows of the preparation of the phosphonate linkage of type **2** and **3** to urea-PETT. The hyroxyl group of urea-PETT **1** is protected with a suitable protecting group, for example, trityl, silyl, benzyl or MOM- etc to give **6** as described in Greene and Wuts, Protecting Groups in Organic Synthesis, 3rd Edition, John Wiley and Sons Inc. The resulting protected Urea-PETT **6** is first treated with a suitable base to remove the urea proton, the product is then treated with 1 equivalent of a phosphonate reagent **5** bearing a leaving group such as, for example, bromine, mesyl, tosyl etc to give the alkylated product **7** and **8**. The phosphonates **7** and **8** are separated by chromatography and independently deprotected using conventional conditions described in Greene and Wuts, Protecting Groups in Organic Synthesis, 3rd Edition, John Wiley and Sons Inc. p116-121. For example (Urea-PETT Example 2), Urea-PETT **1** is protected as t-butyl dimethyl silyl ether **6a** by reacting with TBSCl and imidazole. Compound **6a**, in DMF, is treated with sodium hydride followed by one equivalent of bromomethyl phosphonic acid dibenzyl ester **5.2** to give phosphonate **7a** and **8a** respectively. Phosphonates **7a** and **8a** are separated by chromatography, and then independently deprotected by treatment with TBAF in an aprotic solvent such as THF or acetonitrile to give **3a** and **4a** respectively in which the linkage is a methylene group. Using the above procedure but employing a different phosphonate reagent **5** in place of **5.2**, corresponding products **3** and **4** with different linking groups are obtained.

Urea-PETT Scheme 2



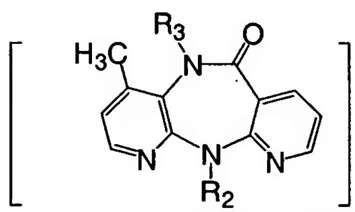
Urea-PETT Example 2

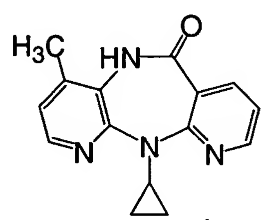




<u>Nevaripine-like phosphonate NNRTI compounds</u>

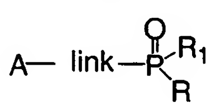
The present invention describes methods for the preparation of phosphonate analogs of nevaripine class of HIV inhibiting agents shown in Nevaripine Illustration 1 that are potential anti-HIV agents.

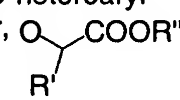
 = A



1

R_2 and R_3 are independently H, C_{1-6} alkyl and C_{1-6} cycloalkyl



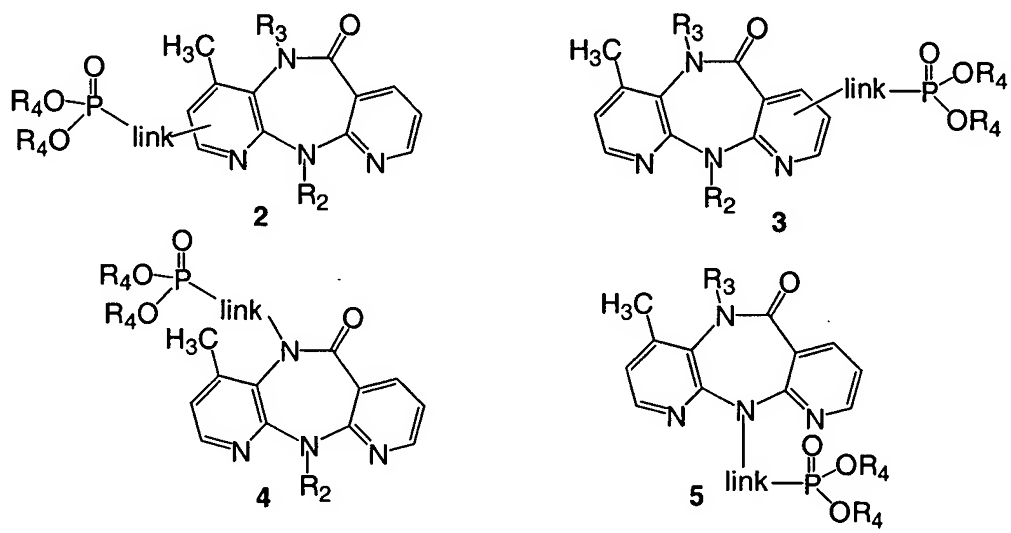
link = linkage group
R = OAr, O-heteroaryl, amino acid ester substituted OAr, O-heteroaryl
R1 = amino acid ester, 

<u>Nevaripine Illustration 1</u>

A link group includes a portion of the structure that links two substructures, one of which is nevapine class of HIV inhibiting agents having the general formula shown above, the other is a phosphonate group bearing the appropriate R and R1 groups. The link has at least one uninterrupted chain of atoms other than hydrogen. Nevirapine-type compounds are inhibitors of HIV RT, and nevirapine is currently used in clinical for treatment of HIV infection and AIDS.

The present invention provides novel analogs of nevirapine class of compound. Such novel nevirapine analogs possess all the utilities of nevirapine and optionally provide cellular accumulation as set forth below.

The intermediate phosphonate esters required for conversion into the prodrug phosphonate moieties bearing amino acid, or lactate esters are shown in Nevaripine Illustration 2.



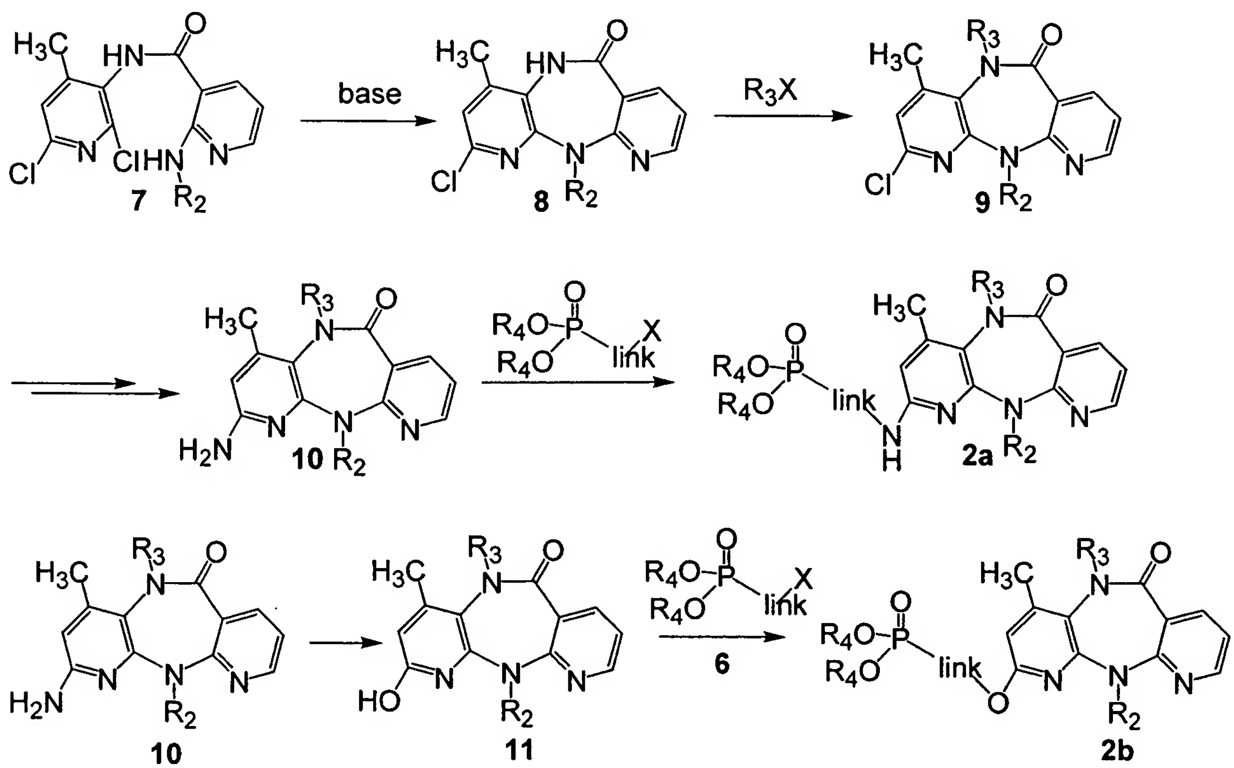
Nevaripine Illustration 2

Compound **1** is synthesized as described in US Patent No. 5366972 and *J. Med. Chem.* **1991**, *34*, 2231. Preparation of phosphonate analog **2** is outlined in Nevaripine Schemes 1 and 2. Amide **7** is prepared as described in US Patent No. 5366972 and *J. Med. Chem.* **1998**, *41*, 2960-2971 and 2972-2984. Amide **7** is converted to dipyridodizaepinone **10** following the procedures described in US Patent No. 5366972 and *J. Med. Chem.* **1998**, *41*, 2960-2971 and 2972-2984. Namely, treatment of dipyridine amide **7** with base provides the dipyridodizaepinone **8**. Alkylation of the amide N- is achieved with base and alkyls bearing a leaving group, such as, for example, bromide, iodide, mesylate, etc. Displacement of chloride with *p*-methoxybenzylamine, followed by removal of the p-methoxybenzyl group affords amine **10**. The amine group serves as the attachment site for introduction of a phosphonate group. Reaction of amine **10** with reagent **6** provides **2** with different linker attached to amine.

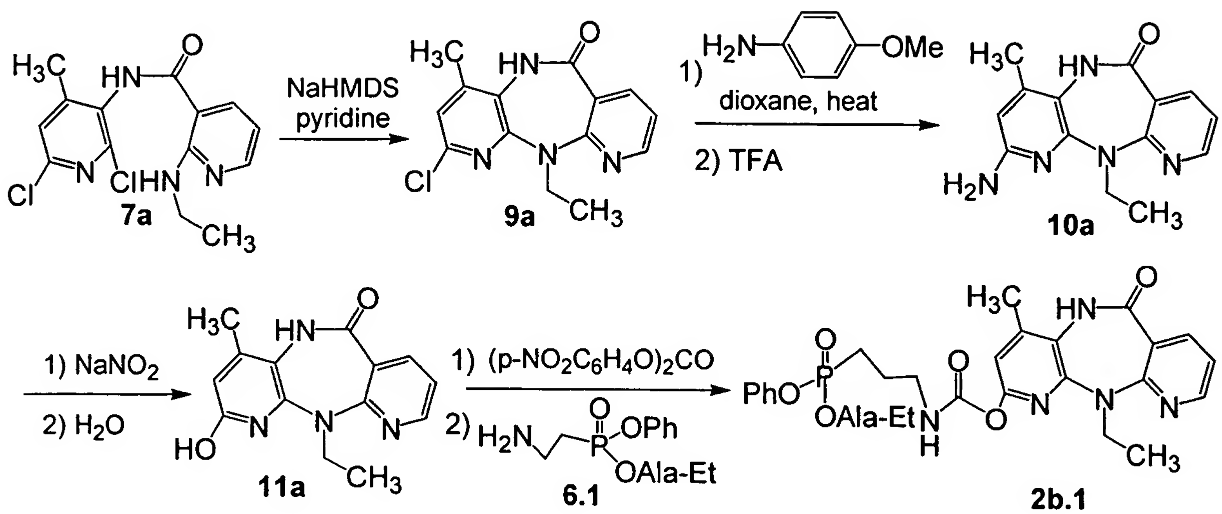
Alternatively (Nevaripine Scheme 2), amine **10** is transformed to phenol **11** as described in *J. Med. Chem.* **1998**, *41*, 2972-2984, many examples are also described in R. C. Larock,

Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed. the hydroxyl group then serves as the linking site for a suitable phosphonate group. Reaction of amine **11** with reagent **6** provides **2** with different linker attached to hydroxyl group. For example (Nevaripine Example 1), amide **7a**, obtained as described in *J. Med. Chem.* **1998**, *41*, 2960-2971 and 2972-2984, is treated with sodium hexamethyldisilazane in pyridine to give diazepinone **9a**. Amine **10a** is synthesized from **9a** by displacement of the chloride with *p*-methoxybenzylamine followed by removal of the protecting group of amine. Diazotization of the amine **10a** and subsequent in situ conversion to hydroxy yields phenol **11a**. Phosphonate with different linker is then able to be attached at the phenol site. For example, the phenol is activated as *p*-nitro-benzyl carbonate, subsequent treatment with amino ethyl phosphonate **6.1** in the presence of Hunig's base affords carbamate **2b.1**.

Nevaripine Scheme 1



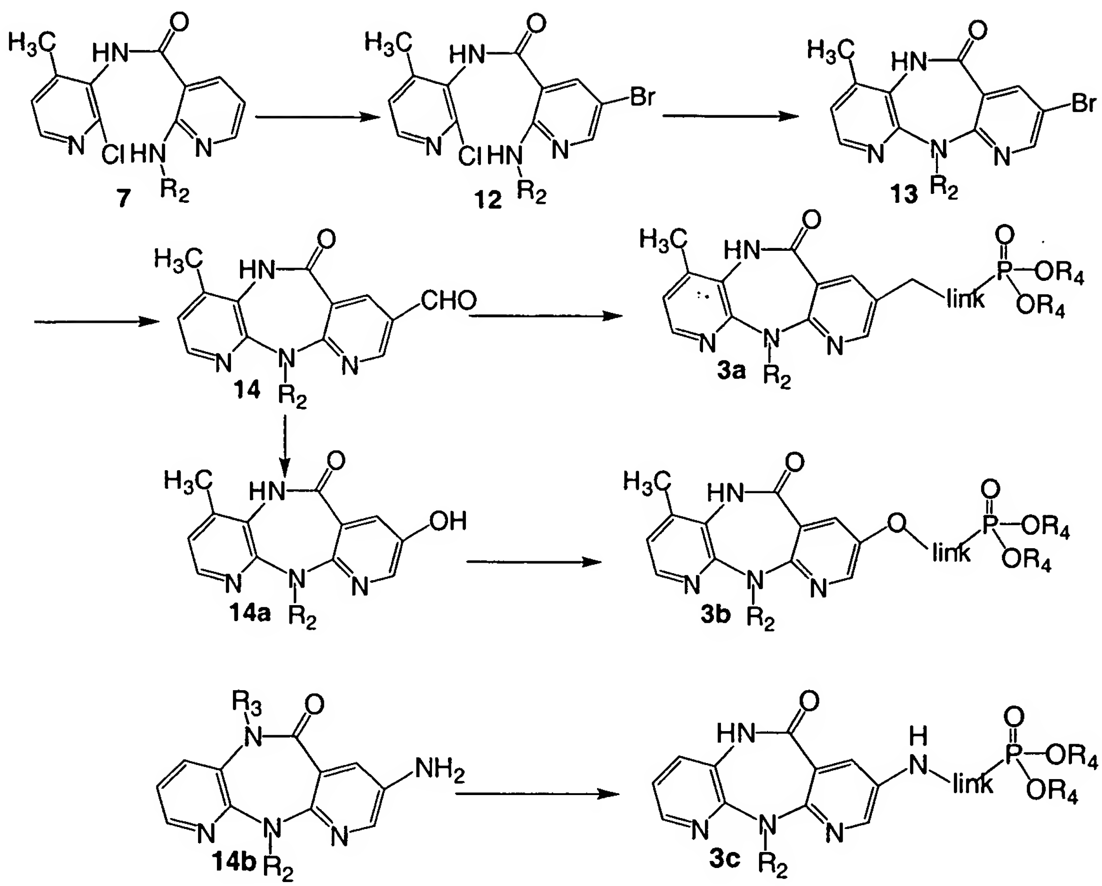
Nevaripine Example 1



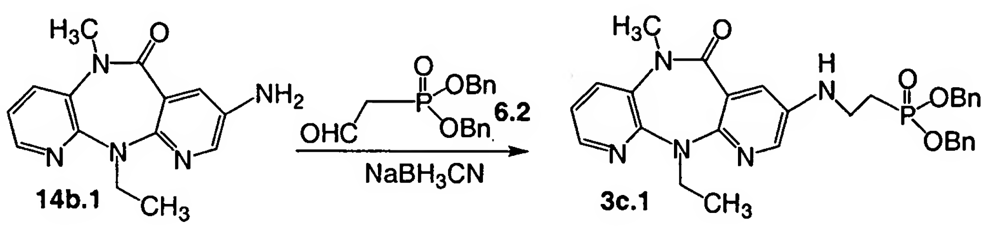
Nevaripine Scheme 2 shows the preparation of phosphonate conjugates compounds type **3** in Nevaripine Illustration 2. Diazapinone **13** is obtained from dipyrido amide **7** following the procedure described in *J. Med. Chem.* **1998**, *41*, 2960-2971 and 2972-2984, which is then converted to aldehyde **14** and phenol **14a** following the procedures in the same literature. Aldehyde **14** and phenol **14a** are then converted to **3a** and **3b** respectively by reacting with suitable phosphonate reagents **6**. Amine **14b** is obtained using the method described in *J. Med. Chem.* **1998**, *41*, 2960-2971, which is converted to phosphonate **3c**.

For example (Nevaripine Example 2), amine **14b.1**, obtained by using the procedures described in *J. Med. Chem.* **1998**, *41*, 2960-2971, reacts with phosphonic acid dibenzyl ester **6.2** under reductive amination conditions to give phosphonate **3c.1**.

Nevaripine Scheme 2



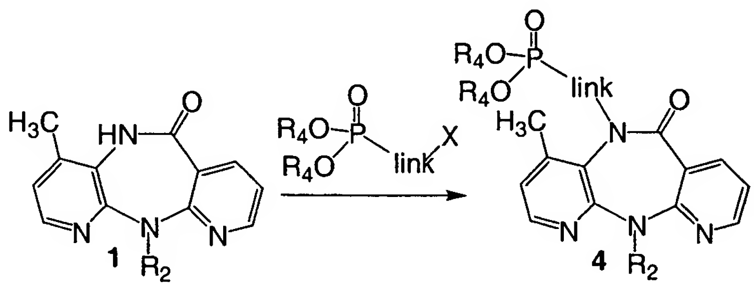
Nevaripine Example 2



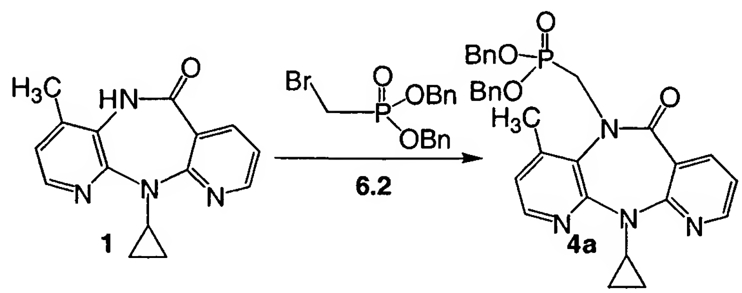
Preparation of phosphonate analog type **4** in Nevaripine Illustration 2 is shown in Nevaripine Scheme 3. Nevaripine analog **1** is dissolved in suitable solvent such as, for example, DMF or other protic solvent, and treated with the phosphonate reagent **9**, bearing a leaving group, such as, for example, bromine, mesyl, tosyl, or triflate, in the presence of a suitable organic or inorganic base, to give phosphonate **4**. For example, **1** was dissolved in DMF, is

treated with sodium hydride and 1 equivalent of bromomethyl phosphonic acid dibenzyl ester **6.2** to give phosphonate **4a** in which the linkage is a methylene group.

Nevaripine Scheme 3



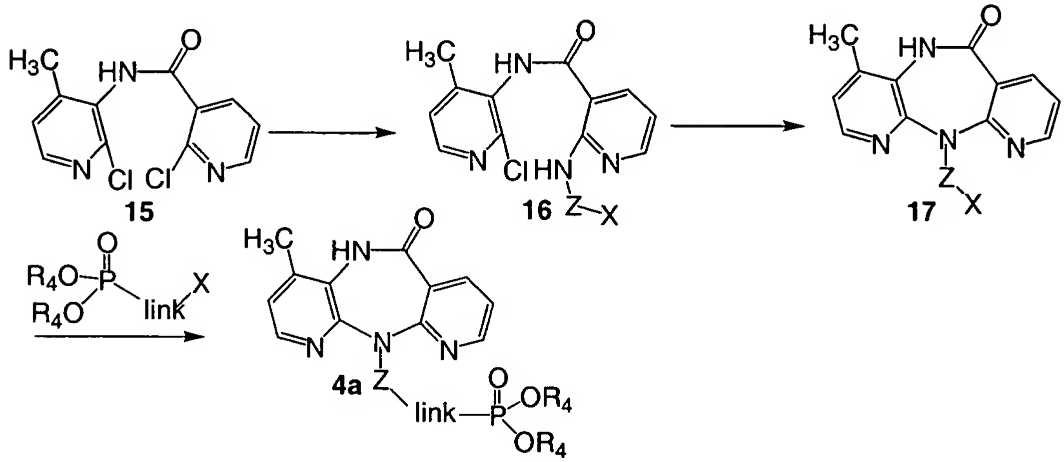
Nevaripine Example 3

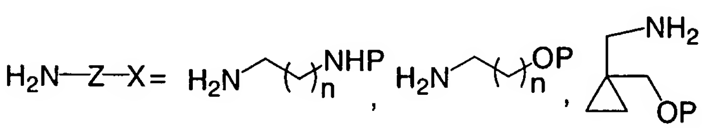


Nevaripine Scheme 4 shows the preparation of phosphonate type **5** in Nevaripine Illustration 2. Amine **15** is prepared according to the procedures described in US Patent No. 5366972 and *J. Med. Chem.* **1998**, *41*, 2960-2971 and 2972-2984. Substituted alkyl amines, which bearing a protected amino or hydroxyl group, or a precursor of amino group, are used in displacement of alkyls described inUS Patent No. 5366972 and *J. Med. Chem.* **1998**, *41*, 2960-2971 and 2972-2984, react with the chloropyridine **15** in the presence of base to give amine **16.** These alkyl amines include but not limit to examples in Nevaripine Scheme 4. These substituted alkyl amines are obtained from commercial sources by protection of the amino or hydroxyl group with a suitable protecting group, for example trityl, silyl, benzyl etc as described in Greene and Wuts, Protecting Groups in Organic Synthesis, 3rd Edition, John Wiley and Sons Inc. Formation of the diazepinone ring in the presence of a suitable base produces **17**. Removal of protecting group or conversion to amine group from a precursor, such as a nitro group, followed by treatment with reagent **6** yield **5a**. For example (Nevaripine Example 4), the hydroxyl group of 2-hydroxy ethylamine is protected as its MOM-ether (**19**). Selective displacement of 2'-

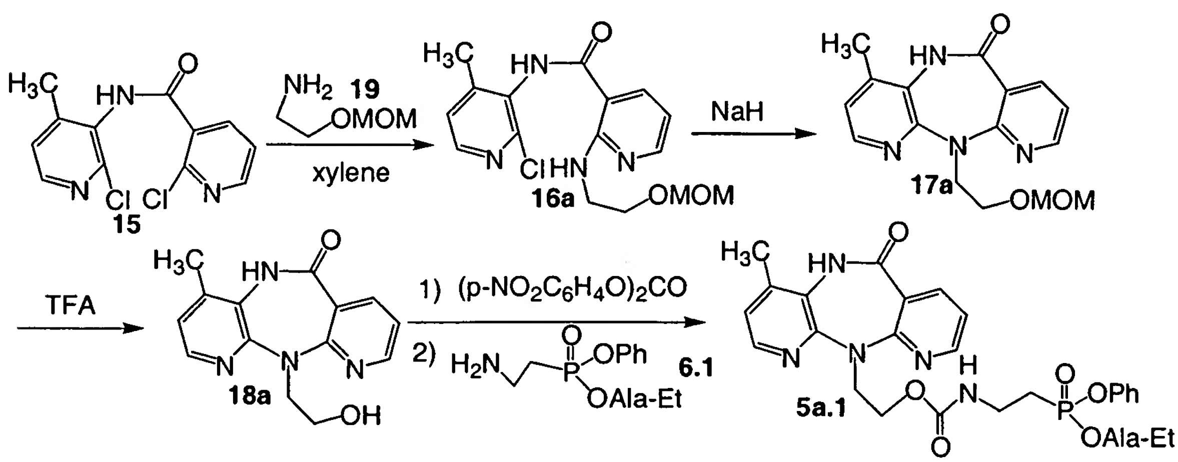
chloro substituent of the pyridinecarboxamide ring with substituted ethylamine **19** produce **16a**. Formation of the diazepinone ring in the presence of sodium hexamethyldisilazane affords **17a**. MOM- is then removed to provide alcohol **18a**. The hydroxyl group is then used for attaching the phosphonate group. The alcohol is first converted to carbonate by reacting with bis(4-nitrobenzyl)carbonate, subsequent treatment of the resulting carbonate with aminoethyl phosphonate **6.2** provides phosphonate **5a.1**.

Nevaripine Scheme 4



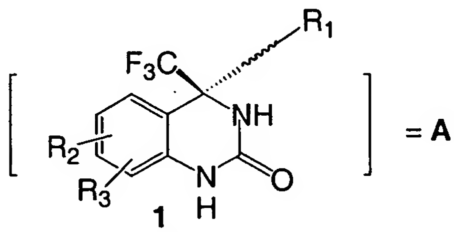


Nevaripine Example 4



Quinazolinone-like phosphonate NNRTI compounds

The present invention describes methods for the preparation of phosphonate analogs of quinazolinones shown in Quinazolinone Illustration 1 that are potential anti-HIV agents.



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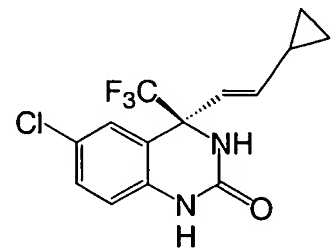


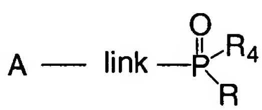
DPC-083

~~~~ = signl, double, triple bond

R_1 = substituted C_{3-5} alkyl, C_{3-5} cycloalkyl phenyl and heterocyclic, substituents are C_{1-4} alkyls, OH, C_{1-4}alkoxyl, halides, NH_2, NHR_1', $NR_1'R_1'$, $NHCOR_1'$

R_2 = H, MeO, F, Cl

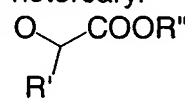
R_3 = H, F,Cl



link = linkage group

R = OAr, O-heteroaryl, amino acid ester substituted OAr, O-heteroaryl

R_4 = amino acid ester,



Quinazolinone Illustration 1

A link group includes a portion of the structure that links two substructures, one of which is quinazolinones having the general formula shown above, the other is a phosphonate group bearing the appropriate R and R_4 groups. The link has at least one uninterrupted chain of atoms other than hydrogen.

Quinazolinone class of compound, act as NNRTI, has demonstrated to inhibit HIV replication. DPC-083, one of representative analogs of this class of compounds, is in clinical phase II studies for treatment of HIV infection and AIDS. The present invention provides novel analogs of quinazolinone class of compound. Such novel quinazolinone analogs possess all the utilities of quinazolinone and optionally provide cellular accumulation as set forth below.

The intermediate phosphonate esters required for conversion into the prodrug phosphonate moieties bearing amino acid, or lactate esters are shown in Quinazolinone Illustration 2.
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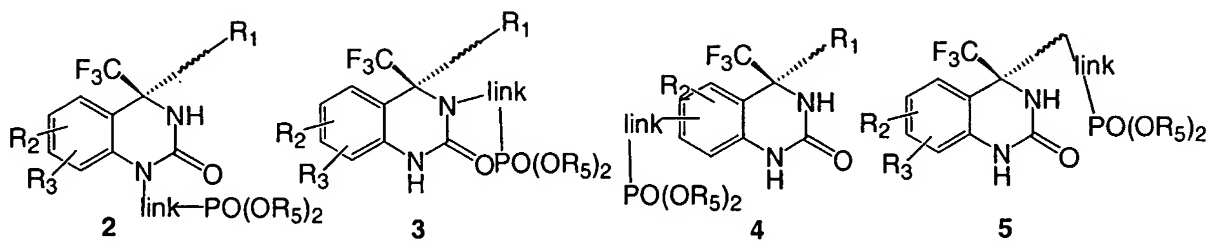
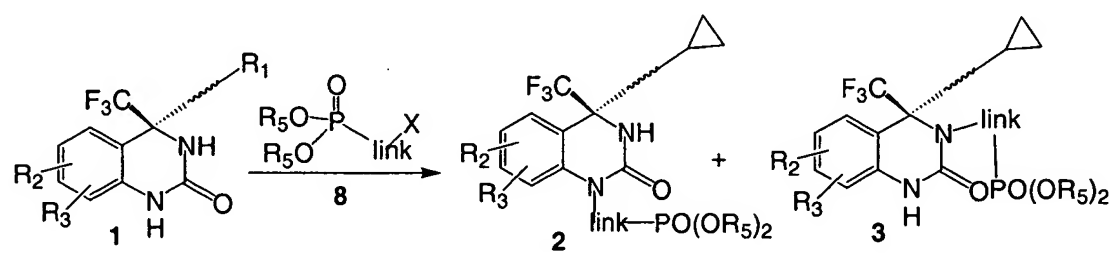


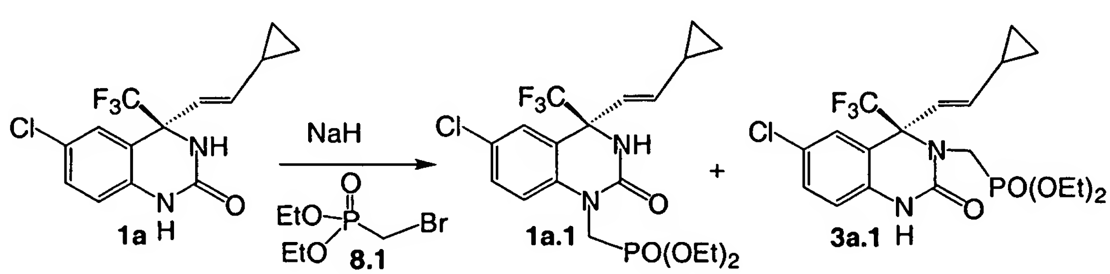
Quinazolinone Illustration 2

Preparation of phosphonate **2** is outlined in Quinazolinone Scheme 1. Quinazolinone **1**, synthesized as described in Patent EP0530994, WO93/04047 and US Patent No. 6423718, is dissolved in suitable solvent such as, for example, DMF or other protic solvent is first treated with a suitable base to remove the urea proton, the product is then treated with 1 equivalent of a phosphonate reagent **8** bearing a leaving group such as, for example, bromine, mesyl, tosyl etc to give the alkylated product **2** and **3**. The phosphonates **2** and **3** are separated by chromatography. For example, **1** is dissolved in DMF, is treated with sodium hydride and 1 equivalent of bromomethyl phosphonic acid diethyl ester **8.1** prepared to give quinazolinone phosphonate **2** in which the linkage is a methylene group. Using the above procedure but employing different phosphonate reagents **8** in place of **8.1**, the corresponding products **2** and **3** are obtained bearing different linking group.

Quinazolinone Scheme 1



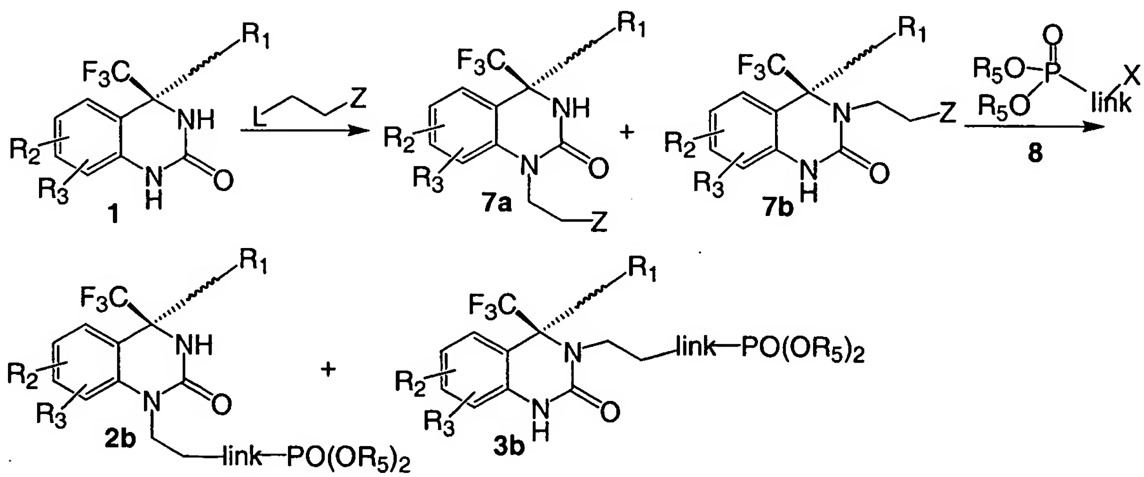
Quinazolinone Example 1



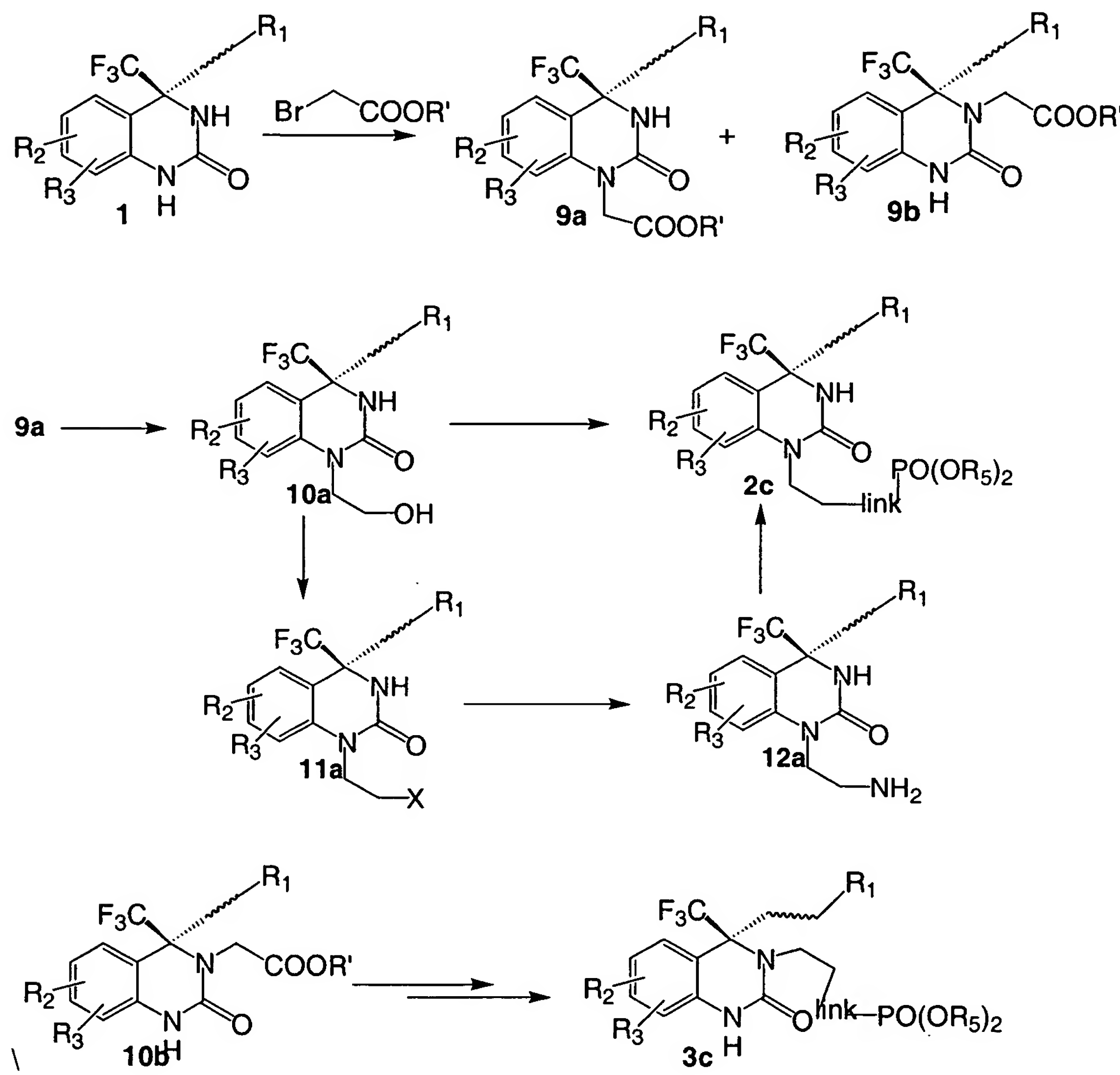
Quinazolinone Scheme 2 shows the preparation of phosphonate analogs type **2** and **3** attached with an alternative way. Quinazolinone **1**, dissolved in a suitable solvent such as, for example, DMF or other protic solvents, is first treated with a suitable base to remove the urea proton, the product is then treated with 1 equivalent of reagent **B**, which bears a leaving group such as, for example, bromine, mesyl, tosyl etc, to give the alkylated product **7a** and **7b**. Compound **B** possesses a protected NH_2 or OH group, or a precursor for them. The alkylated product **7a** and **7b** are separated by chromatography. Protecting group is then removed, and the resulting alcohol or amine then reacts with reagent **8** to afford **2b** and **3b** respectively.

Alternatively (Quinazolinone Scheme 3), alkylation of **1** with bromoacetate provides **9a** and **9b**, which are separated by chromatography. The ester group of **9** is reduced to alcohol to give **10**. The alcohol **11** is also transformed to amine **12** under conventional conditions, many examples are described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed. The hydroxyl group of **10** and amino group of **12** then serve as the attachment site for linking phosphonate to provide **2c**. Similarly, ester **10a** is converted to phosphonate **3c** following the procedures of transformation of **10** to **2c**.

Quinazolinone Scheme 2



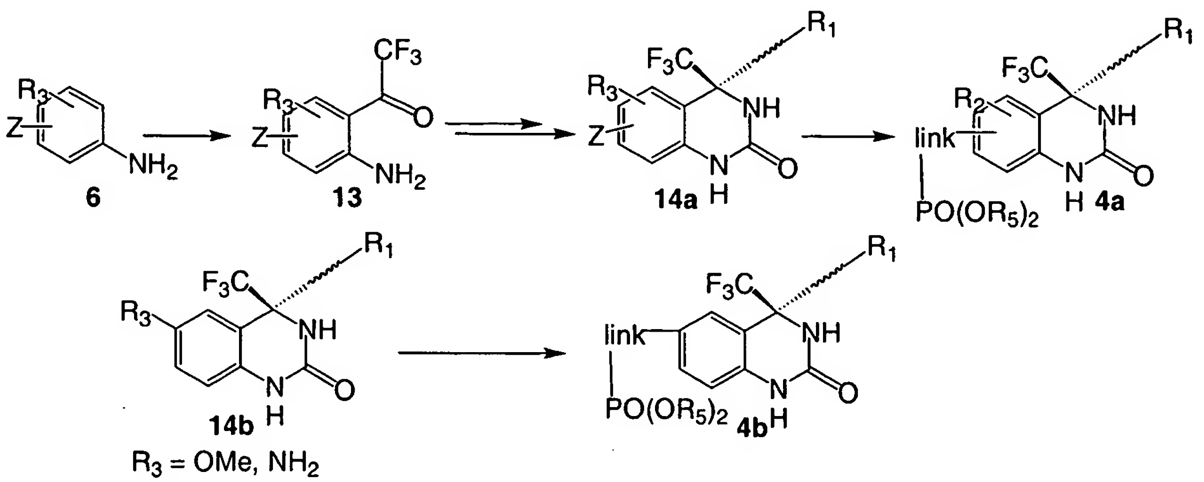
Quinazolinone Scheme 3



Quinazolinone Scheme 4 shows the preparation of quinazolinone-phosphonate conjugates type **4** in Quinazolinone Illustration 2. Substituted aniline **6** with a functional group Z, which is bearing a protected alcohol or amino group, or protected alcohol or amino alkyl, is converted to trifluoromethyl phenyl ketone **13**, which is subsequently converted to quinozolinone **14a**, following the procedure described in US Patent No. 6423718. Deprotection of the protecting group, followed by reacting with reagents **8** under suitable conditions give the desired the phosphonate **4a**. Quinazoline **14b**, prepared according to US Patent No. 6423718, is converted to phosphonate **4b** by reacting with phosphonate reagent **8** directly (R_3=NH_2), or after deprotection (R_3=OMe) under the condition such as for example, BCl_3, many examples are

described in Greene and Wuts, Protecting Groups in Organic Synthesis, 3rd Edition, John Wiley and Sons Inc. Synthesis of compound **6** is described in Quinazolinone Scheme 5.

Quinazolinone Scheme 4



Quinazolinone Scheme 5 shows compounds **6** are obtained through modification of commercial available material 2-halo-5-nitroaniline, or 5-halo-2-nitroaniline (**6.0a**). The amino group of **6.0a** is first protected with a suitable protecting group, for example trityl, Cbz, or Boc etc as described in Greene and Wuts, Protecting Groups in Organic Synthesis, 3rd Edition, John Wiley and Sons Inc. Reduction of the nitro group of **6.1a** with a reducing agent, many examples are described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed, gives **6.1b**, which is then used in the transformation described in Quinazolinone Scheme 4.

The amino group of **6.0a** is converted to hydroxyl group to give **6.2a** by established procedures, for example, diazotization followed by treatment with H_2O/H_2SO4, many examples are described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed. The hydroxyl group is then protected with a suitable protecting group, for example trityl ethers, silyl ethers, methoxy methyl ethers etc as described in Greene and Wuts, Protecting Groups in Organic Synthesis, 3rd Edition, John Wiley and Sons Inc. The nitro group of the resulting compound is then reduced with the above mentioned methods to give **6.2b**, which is then used in the transformation described in Quinazolinone Scheme 4.

The hydroxyl or amino alkyls are obtained using the following methods. The amino group of **6.0a** is converted to nitrile **6.3a** with the known method, for example diazotization followed by treatment with cuprous cyanide, many examples are described in R. C. Larock,

Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed. The nitrile group is then selectively reduced with a reducing agent, many examples are described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed, to give amine **6.3b**. With the mentioned methods above, the amino group is protected and nitro group is reduced respectively to give **6.3c**. Alternatively, the nitrile **6.3a** is converted to acid **6.4a** and the acid is subsequently reduced to alcohol to give **6.4b** using the examples described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed. Similarly, protection of hydroxyl group followed by reduction of nitro to amine gives **6.4c**. Compound **6.3c** and **6.4c** are used in Quinazolinone Scheme 4 respectively.

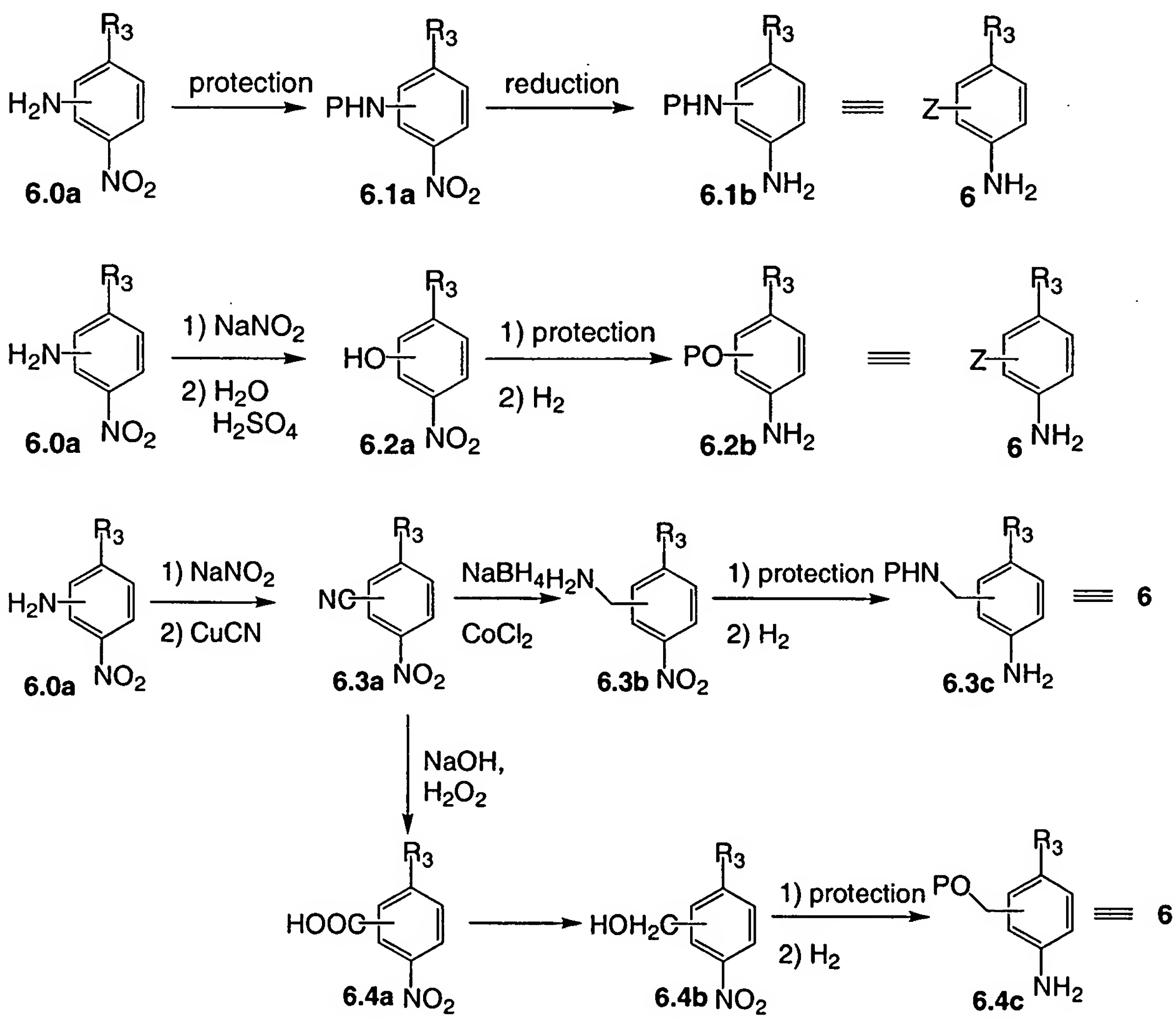
The homologated hydroxyl or amino alkyls are obtained using the following methods (Quinazolinone Scheme 3). The acid **6.4a** are extended to acid **6.5a**, which is transformed to nitrile **6.5b**, these two transformation are described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed, Nitrile **6.5b** is converted to aniline **6.5c** using the similar methods described above. Alternatively, nitrile **6.5b** is obtained by first convert benzyl alcohol **6.4b** to benzyl halide, then treated with CN- nucleophile. Reduction of acid **6.5a** provided alcohol **6.6b**, which is protected using the protecting groups described above to give the required aniline **6.6c**. Compound **6.5c** and **6.6c** are used in Quinazolinone Scheme 4 respectively.

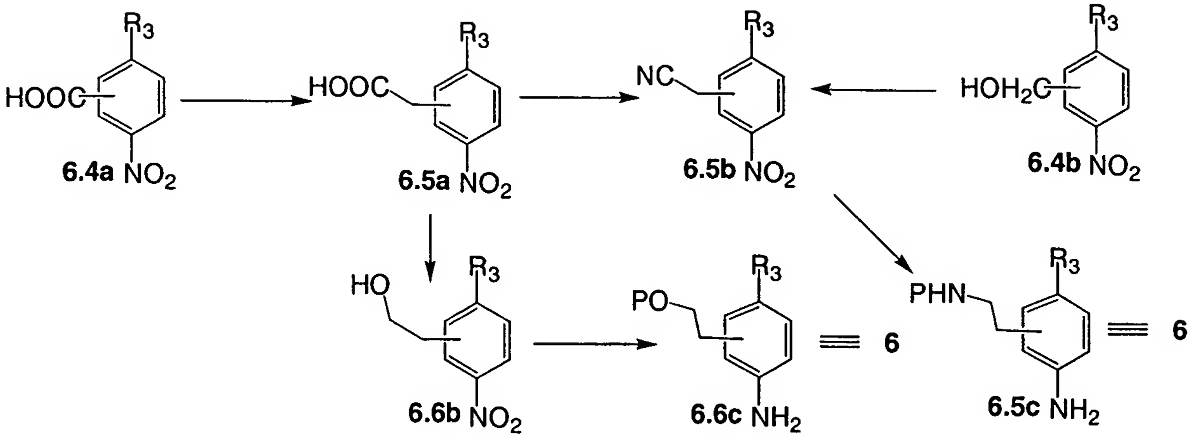
For example aniline **6.0a** (Quinazolinone Example 2) is treated with $NaNO_2$ in the presence of acid at 0°C, then the resulting mixture was heated in H_2O to give phenol **6.2a**. The hydroxyl group is then protected as methoxyl methyl ether by treating phenol **6.2a** with MOMCl in the presence of Hunig's base to yield **6.21b**. Hydrogenation of nitrobenzene affords aniline **6a**. Aniline **6a** is converted to phenyl trifluoromethyl ketone **13a.1**, which is subsequently transformed to quinazolinone analog **14a.1**, using the method described in US Patent No. 6423718. Deprotection of the MOM-ether with trifluoroacidic acid provides phenol **15**. Treatment of **15,** in acetonitrile, with triflate methyl phosphonic acid dibenzyl ester **8.2** in the presence of Cs_2CO_3 gives **4a.1**. Alternatively, reaction of phenol **15** with ethylenediol under the Mitsunobu condition produces **16**. Hydroxyl group of **16** as activated as carbamate, subsequent treatment with amino methyl phosphonate **8.3** affords phosphonate analog **4a.2**.

Quinazolinone Example 3 shows 2-chloro-5-nitro aniline **6.0b** transformed to nitrile **6.31a** by reacting with $NaNO_2$ and then CuCN subsequently. Hydrolysis of nitrile **6.31a** gives

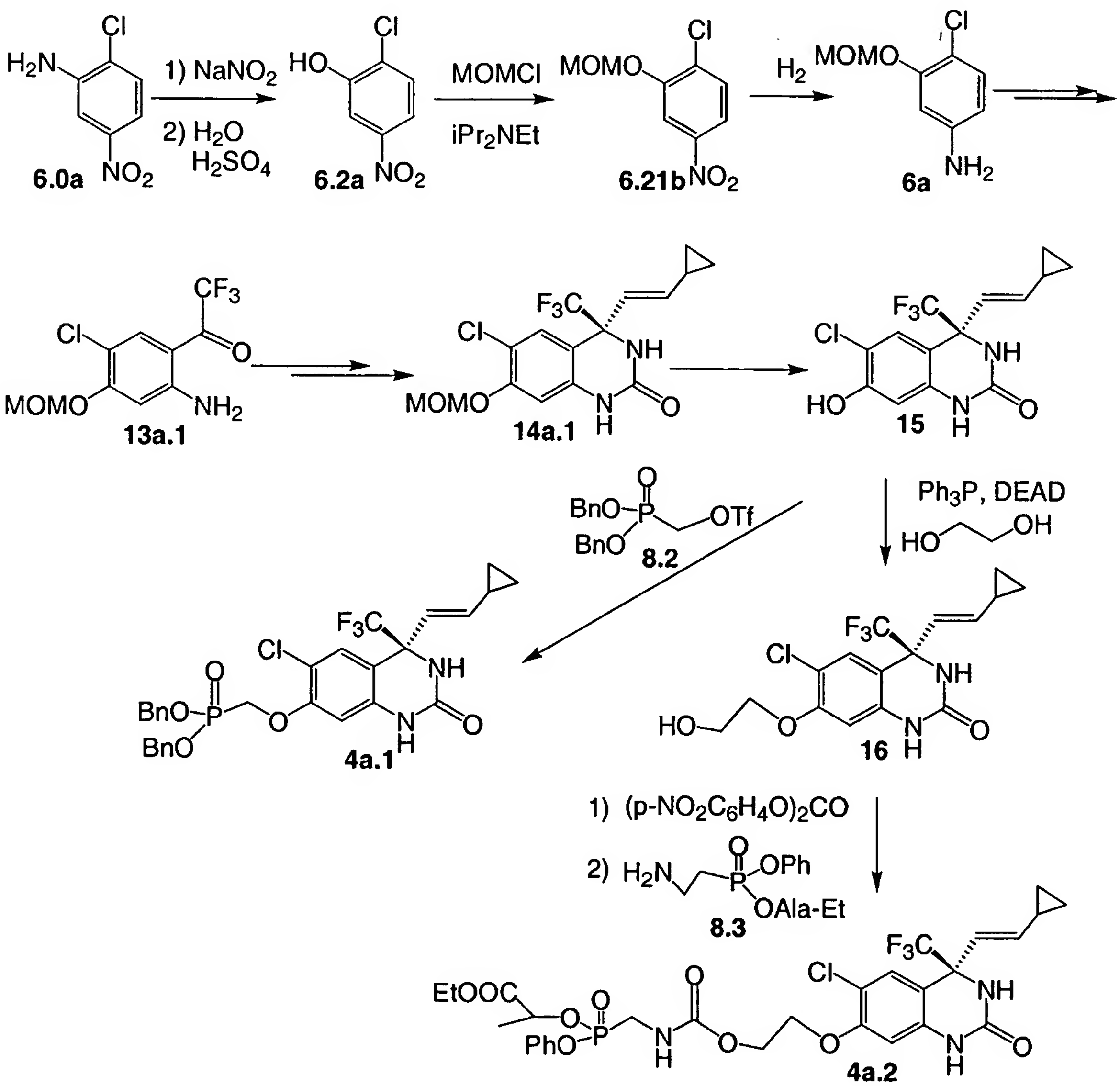
acid **6.41a**. Treatment of **6.41a** with ClCOOEt in the presence of base at 0°C followed by CH_2N_2 provides diazoketone, which is converted to methyl ester **6.51a** upon treating with silver perchlorate in methanol. The ester group is then reduced to give alcohol, which is protected as MOM-ether to provide **6.61c**. The nitro group is then reduced to amine to afford **6b**. Aniline **6b** is converted to quinazolinone analog **14** using the method described in US Patent No. 6423718. Deprotection of the MOM-ether with trifluoroacidic acid provide alcohol **16**. The aldehyde **17** is obtained by oxidation of alcohol. Reductive amination of **17** with amino ethyl phosphonate **8.4** afford analog **4a.3**.

Quinazolinone Scheme 5

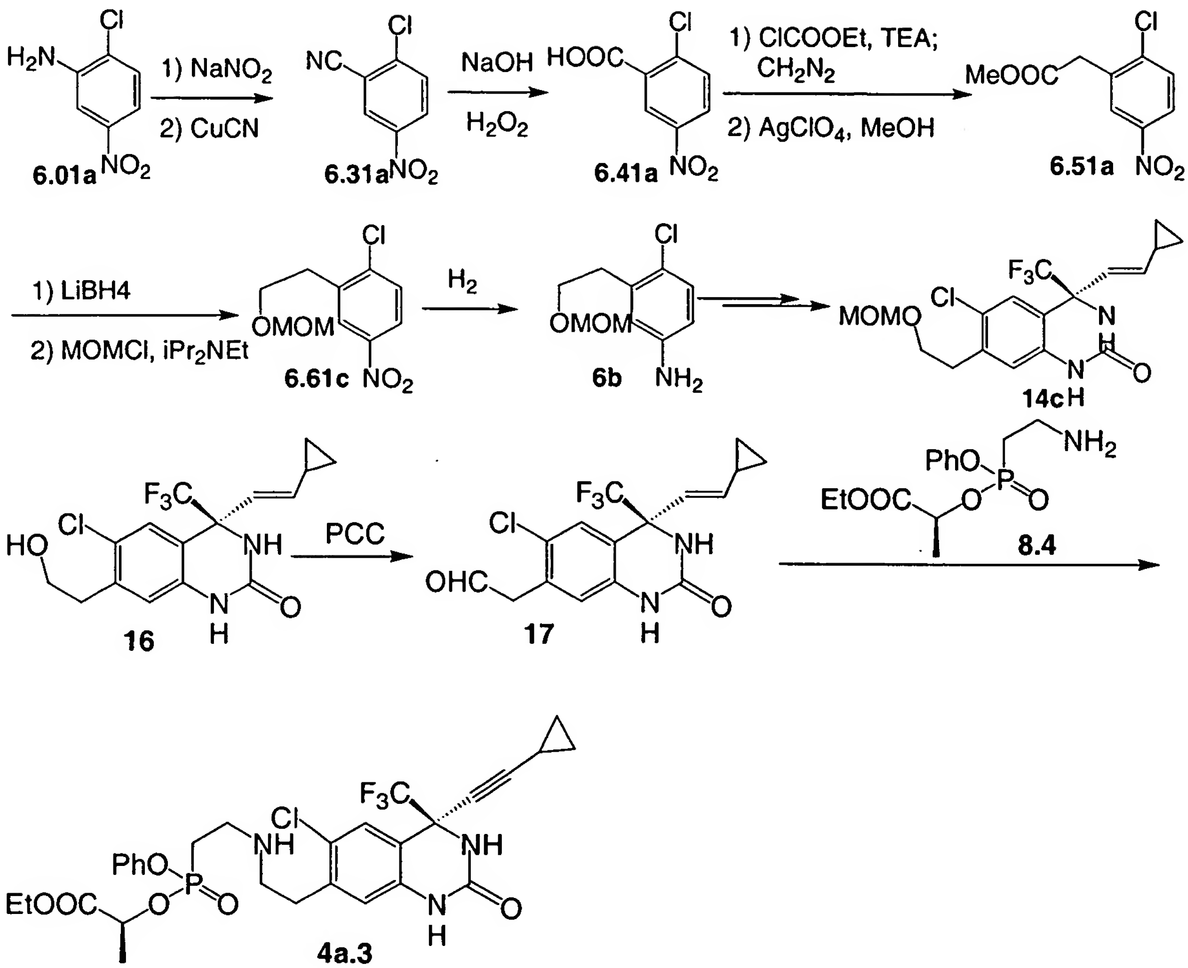




Quinazolinone Example 2

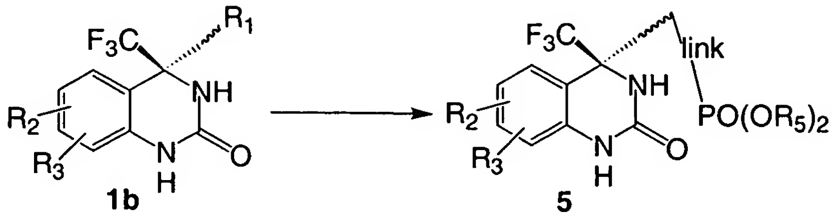


Quinazolinone Example 3



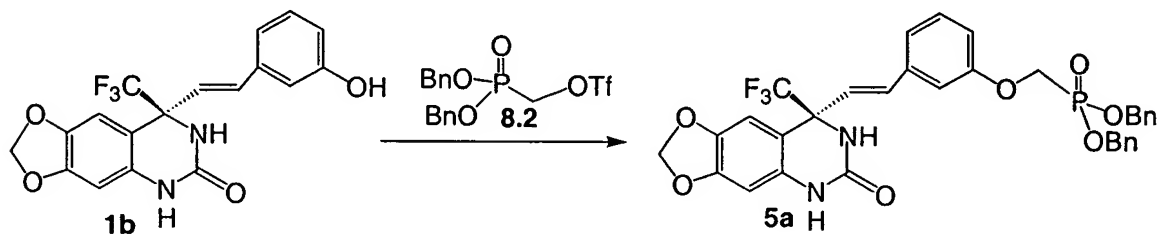
Preparation of phosphonate analog type **5** from quinazolinone **1** is outlined in Quinazolinone Scheme 6. Quinazolinone **1**, which R_1 contains OH, or NH_2 or NHR_1' as the attachment site for connecting phosphonate, reacts with reagent **8** under suitable conditions to provide phosphonate analog 5. For example (Quinazolinone Example 4), Quinozalinone **1b.1**, obtained as described in US Patent No. 6423718, is treated with phosphonate reagents **8.2** in the presence of Cs_2CO_3, give phosphonate **5a**.

Quinazolinone Scheme 3



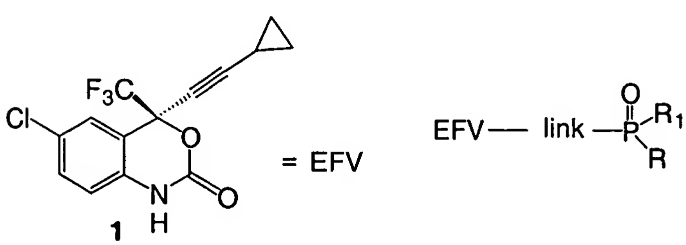
R_1: defined as above but contains OH, NH_2

Quinazolinone Example 4

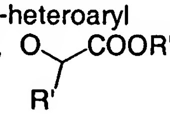


Efavirenz-like phosphonate NNRTI compounds

The present invention includes efavirenz-like phosphonate NNRTI compounds and methods for the preparation of efavirenz phosphonate analogs shown in Efavirenz Illustration 1.



link = linkage group
R = OAr, O-heteroaryl, amino acid ester substituted OAr, O-heteroaryl
R1 = amino acid ester,



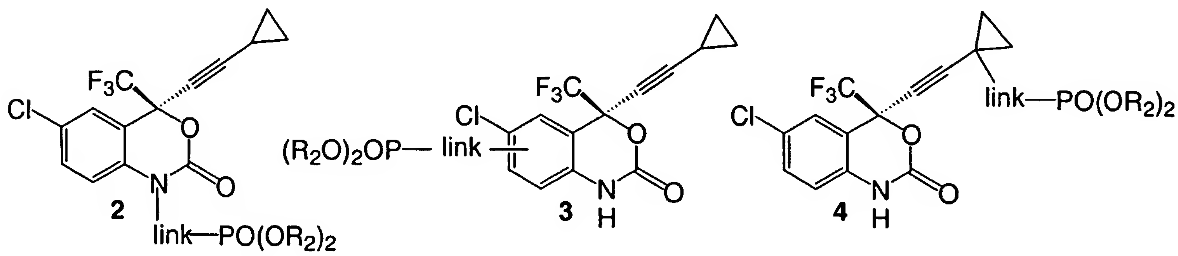
Efavirenz Illustration 1

A link group includes a portion of the structure that links two substructures, one of which is efavirenz having the general formula shown above, the other is a phosphonate group bearing the appropriate R and R_1 groups. The link has at least one uninterrupted chain of atoms other than hydrogen.

Efavirenz and its analogs have demonstrated therapeutic acitivity against HIV replication, and efavirenz is currently used in clinical for treatment of HIV infection and AIDS. The present

invention provides novel analogs of efavirenz. Such novel efavirenz analogs possess all the utilities of efavirenz and optionally provide cellular accumulation as set forth below.

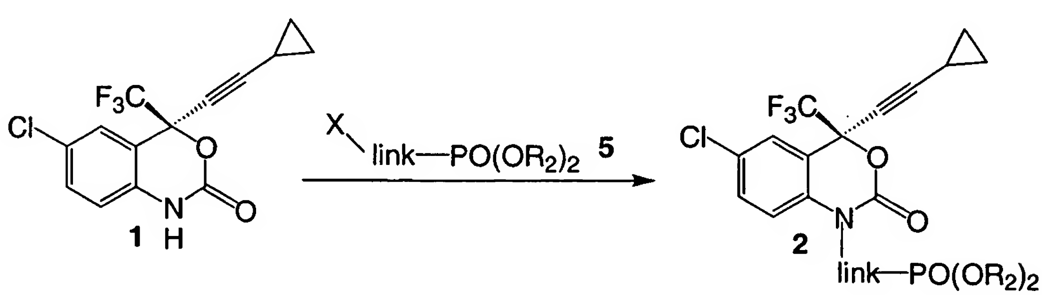
The intermediate phosphonate esters required for conversion into the prodrug phosphonate moieties bearing amino acid, or lactate esters are shown in Efavirenz Illustration 2.



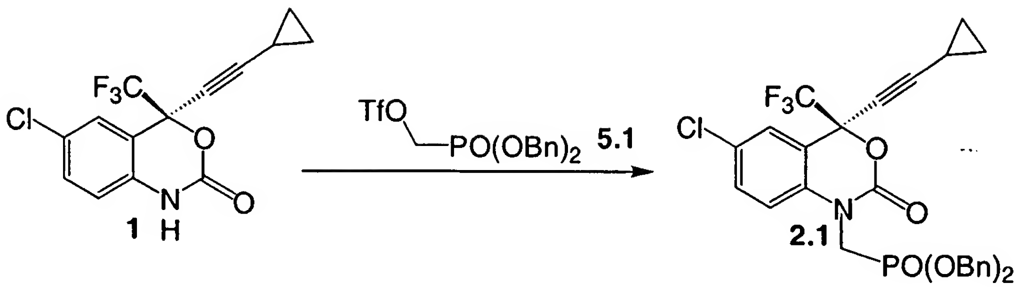
Efavirenz Illustration 2

Compound **1** can be synthesized as described in US Patent No. 5519021. Preparation of compound **2** from efavirenz **1** is outlined in Efavirenz Scheme 1. Efavirenz **1** is dissolved in . suitable solvent such as, for example, DMF or other protic solvent, and treated with the phosphonate reagent **5** in the presence of a suitable organic or inorganic base. For example, **1** is dissolved in DMF, is treated with sodium hydride and 1 equivalent of triflate methyl phosphonic acid dibenzyl ester **5.1** prepared to give EFV phosphonate **2** in which the linkage is a methylene group. Using the above procedure but employing different phosphonate reagents **5** in place of **5.1**, the corresponding products **2** are obtained bearing different linking group.

Efavirenz Scheme 1

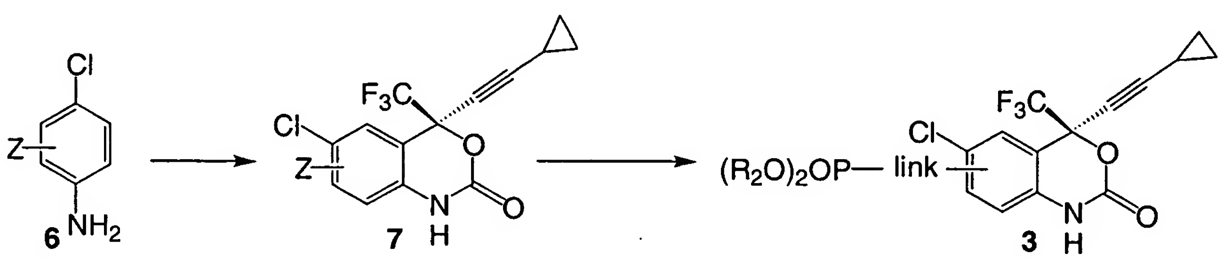


Efavirenz Example 1



Efavirenz Scheme 2 shows the preparation of EFV-phosphonate conjugates compounds **3** in Efavirenz Illustration 2. *p*-Chloro aniline with functional group Z, which bears a protected alcohol or amino group, or protected alcohol or amino alkyl, is converted to compound **7** following the procedure described in US Patent No. 5519021. Deprotection of the protecting group, followed by reacting with reagent **5** in the above mentioned conditions give the desired the compound **3**. As shown in Efavirenz Scheme 3, compounds **6** are obtained through modification of commercial available material 2-chloro-5-nitroaniline, or 5-chloro-2-nitroaniline (**6.0a**).

Efavirenz Scheme 2



The amino group of **6.0a** is first protected with a suitable protecting group (Efavirenz Scheme 3), for example trityl, Cbz, or Boc etc as described in Greene and Wuts, Protecting Groups in Organic Synthesis, 3rd Edition, John Wiley and Sons Inc. Reduction of the nitro group in **6.1a** with a reducing agent, many examples are described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed, give **6.1b**, which is then used in the transformation described in Efavirenz Scheme 2.

Alternatively, the amino group of **6.0a** is converted to hydroxyl group to give **6.2a** by established procedures, for example, diazotization followed by treatment with H_2O/H_2SO_4, many

examples are described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed. The hydroxyl group is then protected with a suitable protecting group, for example trityl ethers, silyl ethers, methoxy methyl ethers etc as described in Greene and Wuts, Protecting Groups in Organic Synthesis, 3rd Edition, John Wiley and Sons Inc. The nitro group of the resulting compound is then reduced with the above mentioned methods to give **6.2b**, which is then used in the transformation described in Efavirenz Scheme 2.

The hydroxyl or amino alkyls are obtained using the following methods. The amino group in **6.0a** is converted to nitrile **6.3a** with the known method, for example diazotization followed by treatment with cuprous cyanide, many examples are described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed. The nitrile group is then selectively reduced with a reducing agent, many examples are described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed, to give amine **6.3b**. With the mentioned methods above, the amino group is protected and nitro group is reduced respectively to give **6.3c**. In addition, the nitrile **6.3a** is converted to acid **6.4a** and the acid is subsequently reduced to alcohol to give **6.4b**, and the reduction of nitro to amine give **6.4c**, using the methods described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed. Both **6.3c** and **6.4c** used in the transformation described in Efavirenz Scheme 2.

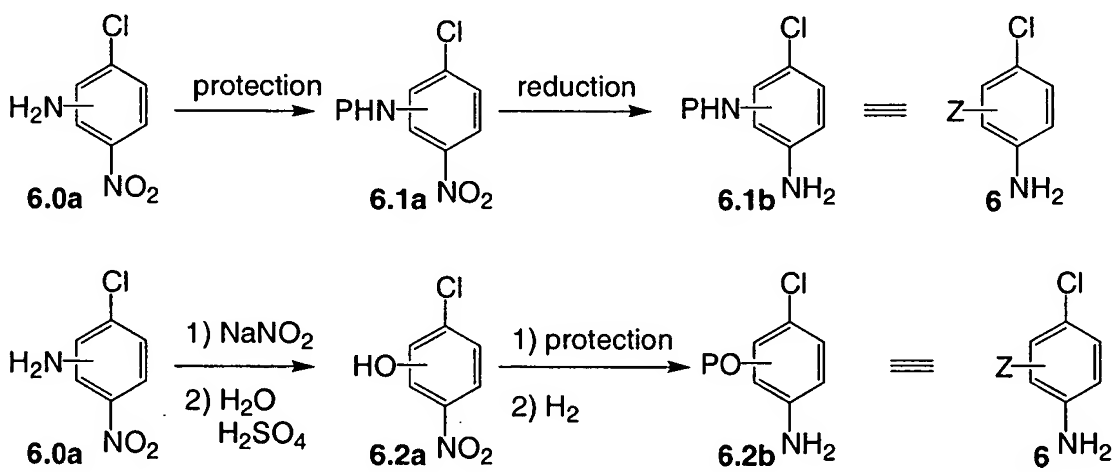
The homologated hydroxyl or amino alkyls are obtained using the following methods (Efavirenz Scheme 3). The acid **6.4a** are extended to acid **6.5a**, which is transformed to nitrile **6.5b**, these two transformation are described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed, Nitrile **6.5b** is converted to aniline **6.5c** using the similar methods described above. Alternatively, nitrile **6.5b** is obtained by first convert benzyl alcohol **6.4b** to benzyl halide, then treated with CN- nucleophile. Reduction of acid **6.5a** provided alcohol **6.6b**, which is protected using the protecting groups described above to give the required aniline **6.6c**. Both **6.5c** and **6.6c** used in the transformation described in Efavirenz Scheme 2.

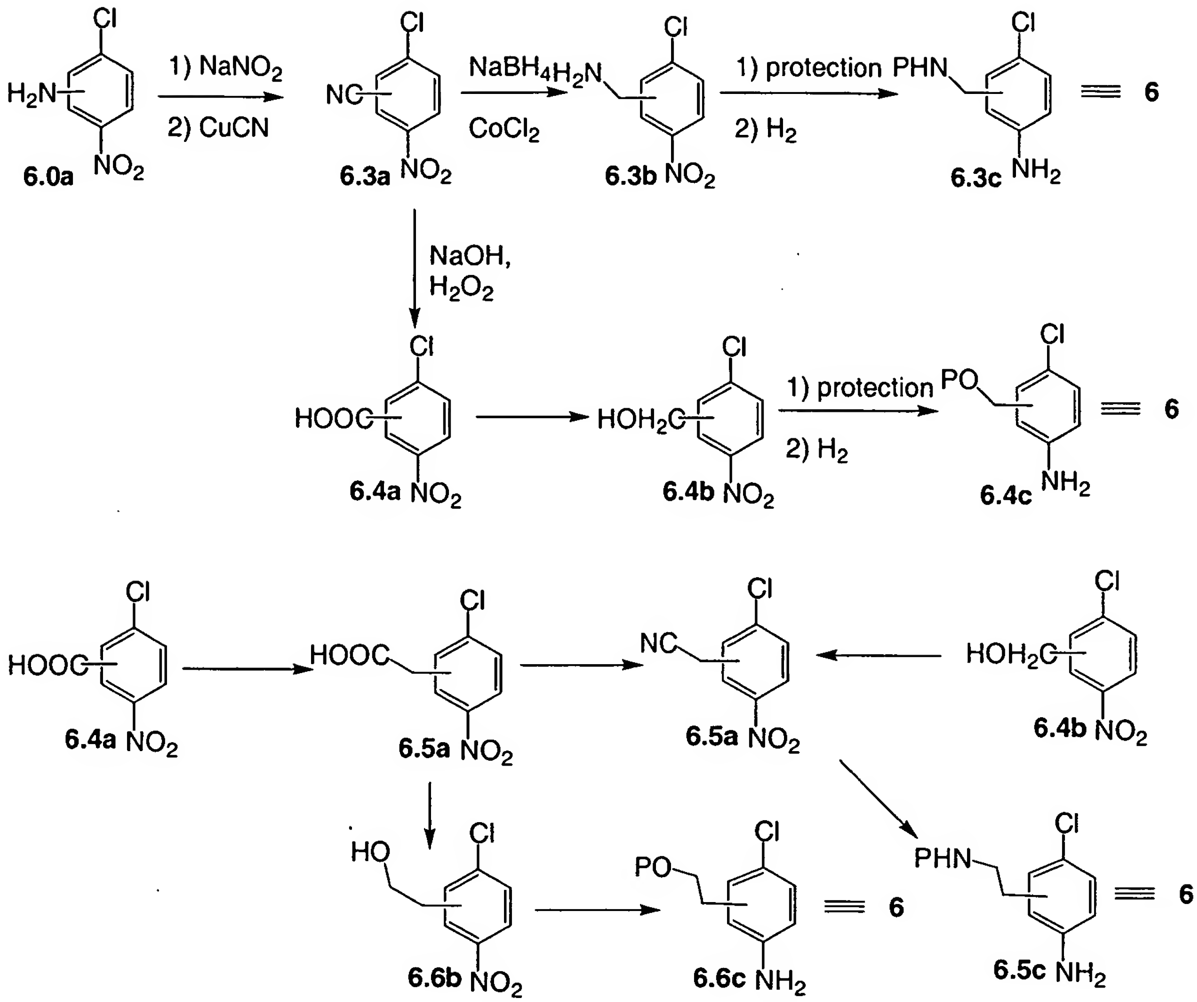
For example aniline **6.0a** (Efavirenz Example 2) is treated with $NaNO_2$ in the presence of acid at 0°C, then the resulting mixture was heated in H_2O to give phenol **6.2a**. The hydroxyl group is then protected as methoxyl methyl ether by treating phenol **6.2a** with MOMCl in the presence of Hunig's base to yield **6.21b**. Hydrogenation of nitrobenzene affords aniline **6.2a**. Aniline **6a** is converted to efavirenz analog **7.1**. Deprotection of the MOM-ether with

trifluoroacidic acid provides phenol **8**. Treatment of **8** in acetonitrile with (trifluorosulfonylmethyl)-phosphonic acid dibenzyl ester **5.1** in the presence of Cs_2CO_3 gives **3a**.

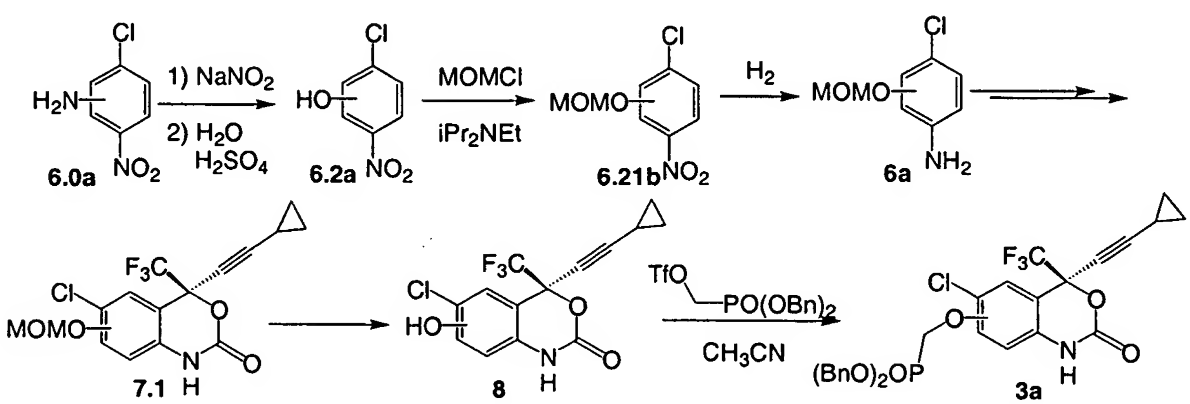
In Efavirenz Example 3, 2-chloro-5-nitro aniline **6.0b** is transformed to nitrile **6.31a** by reacting with $NaNO_2$ and then CuCN subsequently. Hydrolysis of nitrile **6.31a** gives acid **6.41a**. Treatment of **6.41a** with ClCOOEt in the presence of base at 0°C followed by CH_2N_2 provides diazoketone, which is converted to methyl ester **6.51a** upon treating with silver perchlorate in methanol. The ester group is then reduced to give alcohol, which is protected as MOM-ether to provide **6.61c**. The nitro group is then reduced to amine to afford **6b**. Aniline **6a** is converted to efavirenz analog **7.1**. Deprotection of the MOM-ether with trifluoroacetic acid provides phenol **9**. The aldehyde **10** is obtained by oxidation of alcohol. Reductive amination of **10** with agent **5.2** affords analog **3b**.

Efavirenz Scheme 3

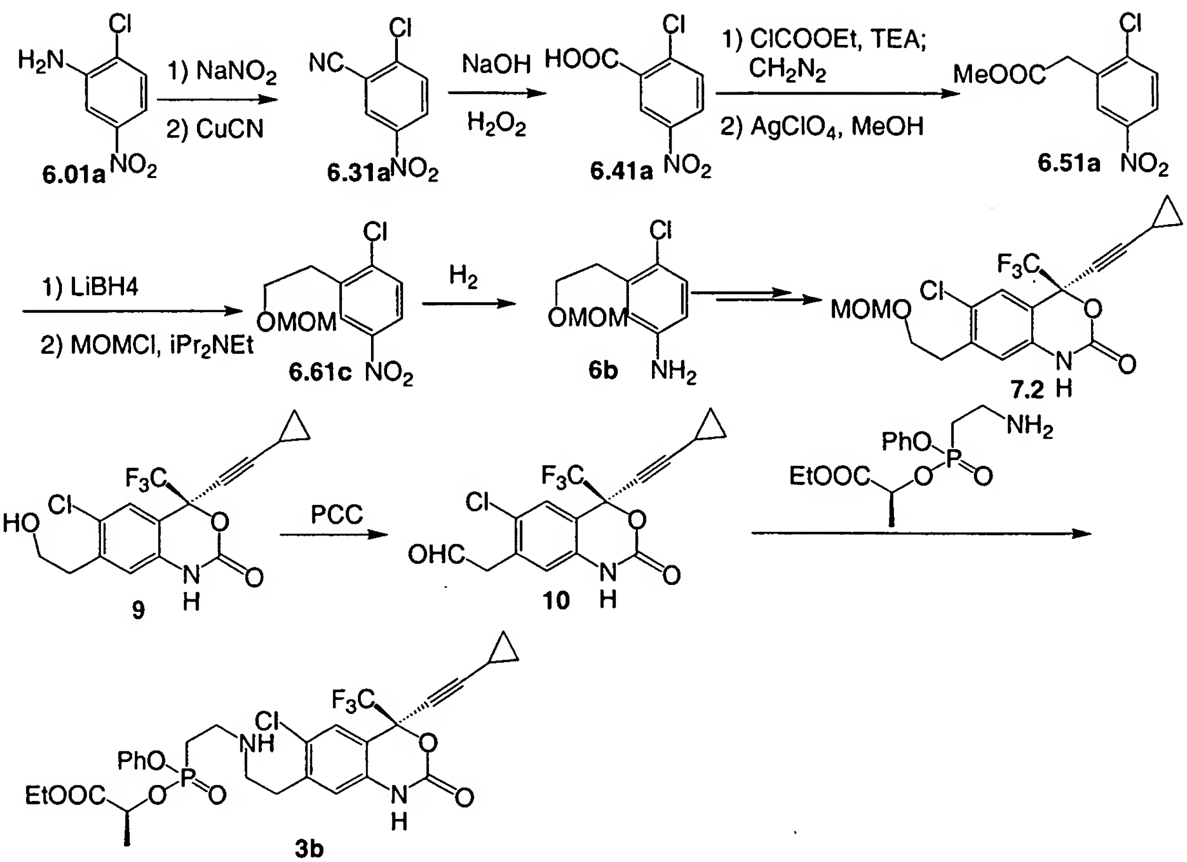




Efavirenz Example 2

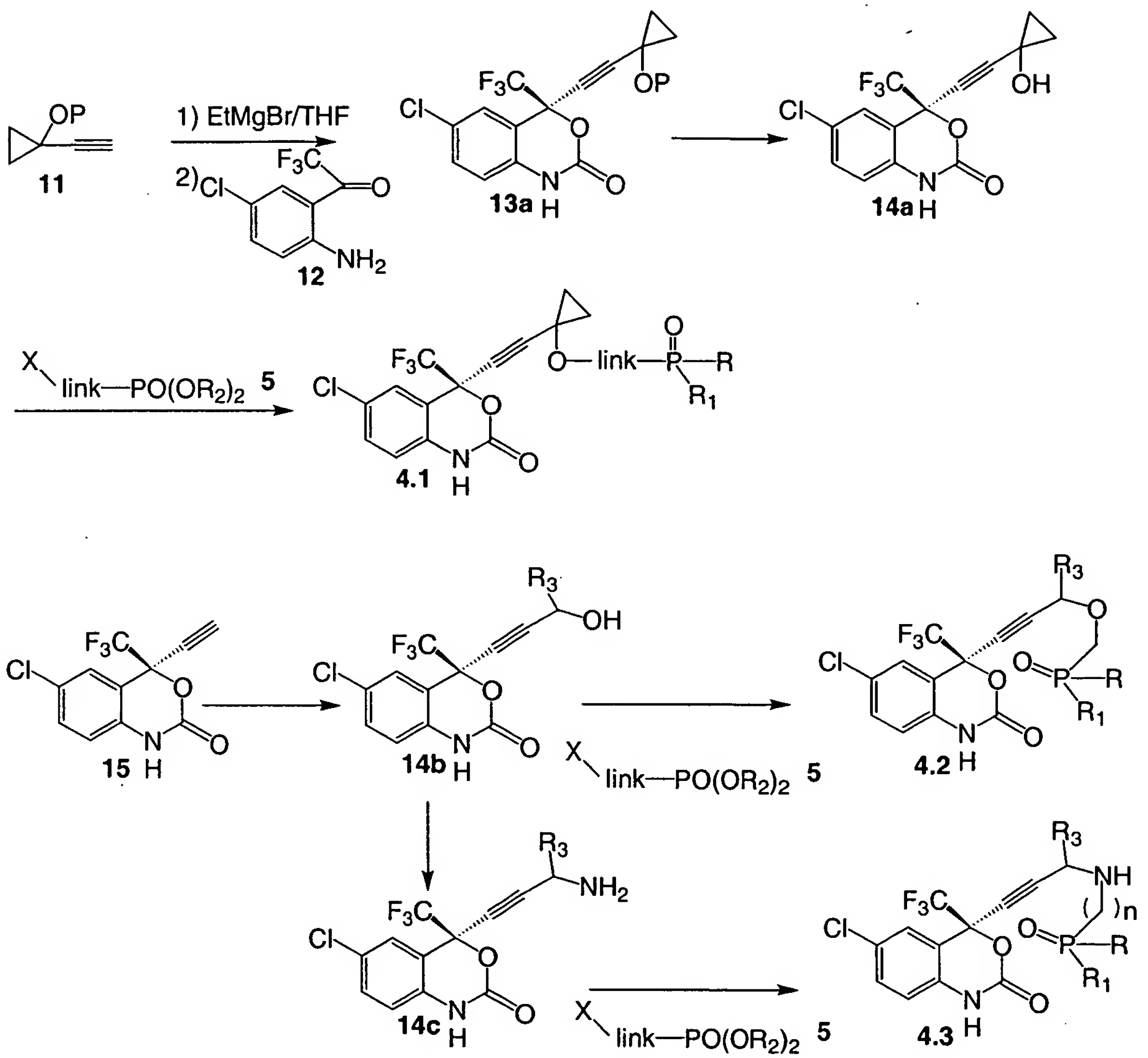


Efavirenz Example 3

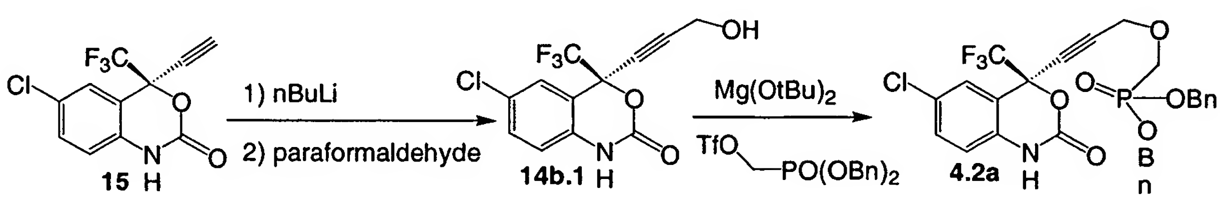


Preparation of compound **2** from efavirenz **1** is outlined in Efavirenz Scheme 4. Compound **12**, obtained as described in US Patent No. 5519021, reacting with Grignard reagent, generated from protected acetylene **11** following the procedure described in US Patent No. 5519021, gives compound **13a**. The hydroxyl group in **11** is protected as its silyl ether, trityl ether, etc. Removal of the protecting group of **13a** yields alcohol **14a**. Alkylation of **14a** with agent **5** affords phosphonate **4.1**. Alternatively, compound **15**, obtained as described in US Patent No. 5519021, reacts with aldehyde or ketone to give alcohol **14b**, which is converted to analog **4b** using the conditions described above. Amine **14c** is obtained from alcohol **14b** under the standard conditions. Amine **14c** is converted to phosphonate **4c** either by reacting with agent **5** or reductive amination with a phosphonate reagents containing an aldehyde group. For example, treatment of compound **14** with n-BuLi followed by paraformaldehyde gives alcohol **14b.1**. Treatment of alcohol **14b.1** with $Mg(OtBu)_2$ followed by phosphonate provides phosphonate **4.2b**.

Efavirenz Scheme 4

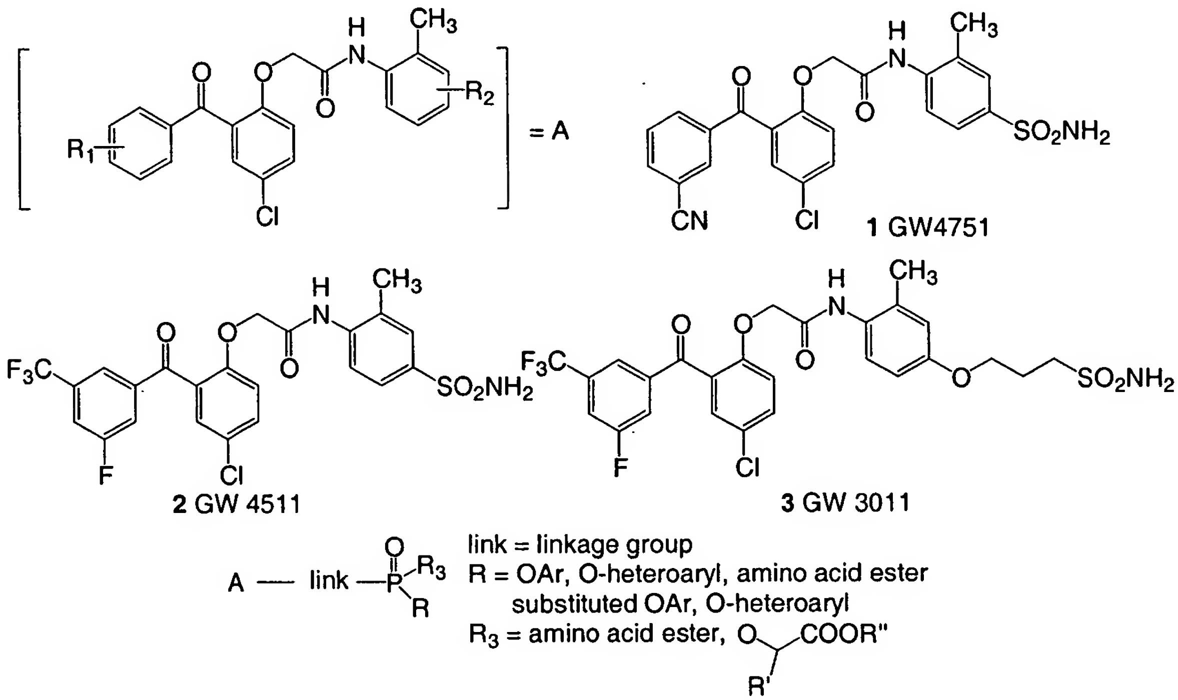


Efavirenz Example 4



Benzophenone-like phosphonate NNRTI compounds

The present invention describes methods for the preparation of phosphonate analogs of benzophenone class of HIV inhibiting pyrimidines shown in Benzophenone Illustration 1 that are potential anti-HIV agents.



R_1 = halide, CF_3, CN, NO_2, C_{1-6} alkyl, OR^1, NHR^1, NHR^1R^2, where R^1 and R^2 are C_{1-6} alkyl

R_2 = OH, OR^1, NHR^1, NHR^1R^2, SO_2NH_2, SO_2NHR^1, $SONR^1R^2$, $CONH_2$, $CONHR^1$, OR^3 where R^3 is H or R_1

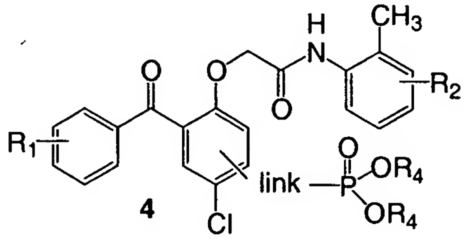
Benzophenone Illustration 1

A link group includes a portion of the structure that links two substructures, one of which is benzophenone class of HIV inhibiting agents having the general formula shown above, the other is a phosphonate group bearing the appropriate R and R_3 groups. The link has at least one uninterrupted chain of atoms other than hydrogen.

Benzophenone class of compounds has shown to be inhibitors of HIV RT. The present invention provides novel analogs of benzophenone class of compound. Such novel

benzophenone analogs possess all the utilities of benzophenone and optionally provide cellular accumulation as set forth below.

The intermediate phosphonate esters required for conversion into the prodrug phosphonate moieties bearing amino acid, or lactate esters are shown in Benzophenone Illustration 2.



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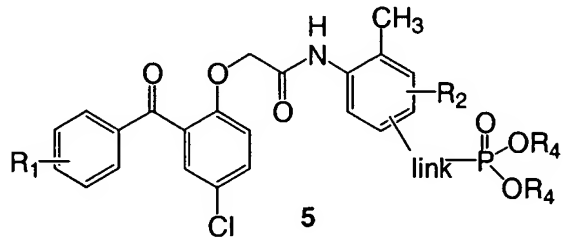

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Benzophenone Illustration 2

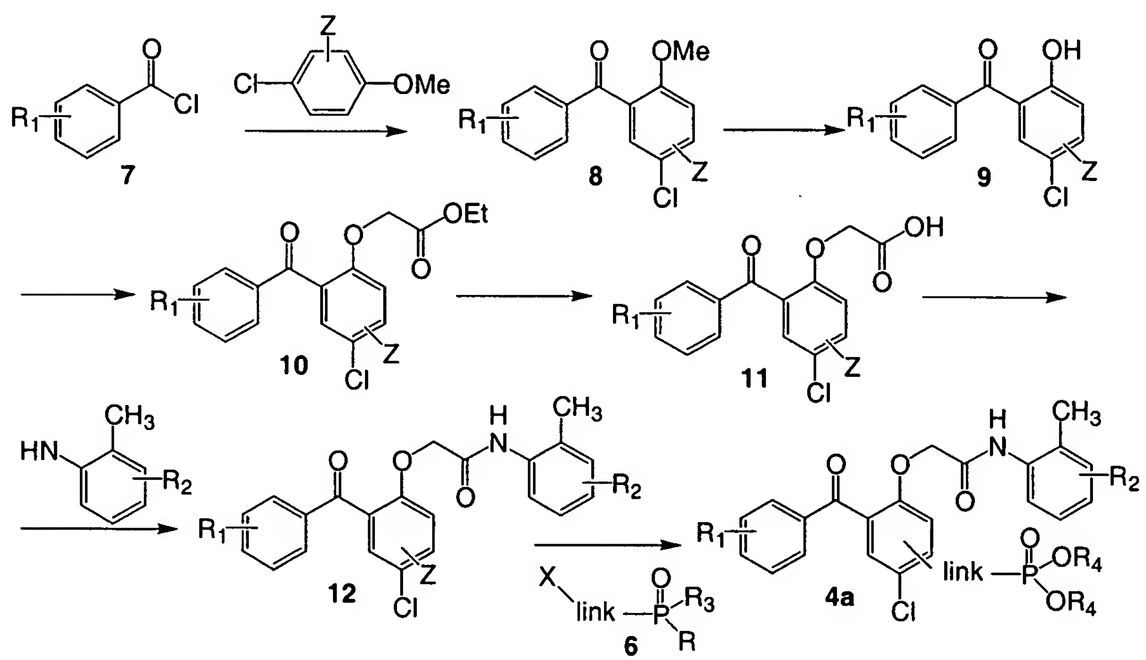
Preparation of phosphonate analog **4** is outlined in Benzophenone Scheme 1. Benzophenone **8** is obtained from Freidel-Crafts reaction of substituted benzoyl chloride **7** and 4-chloro-phenol methyl ether which bearing a protected amine or hydroxyl group Z. Phenol ether is obtained by selective protection of commercially available 4-chlorophenol substituted with amino- or hydroxyl group. Benzoyl chloride is obtained either from commercial sources or prepared from commercial available benzoic acid. Benzophenone **8** is also obtained from oxidation of the corresponding alcohol, which in turn is obtained from the reaction of benzaldehyde and anion. Removal of methyl provides phenol **9**. Alkylation of phenol with bromoacetate such as ethyl bromoacetate affords ester **10**. The ester is then converted to acid. Formation of amide **12** from acid **11** and aniline **10** is achieved following the standard amide formation methods, many examples are described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed. Removal of the protecting group of Z followed by reacting with reagent **6** affords phosphonate analog **4a**.

For example (Benzophenone Example 1), commercially available 3-cyanobenzoyl chloride is treated with trichloroaluminum followed by 3,4-dimethoxy chlorobenzene to give benzophenone **8a**. Treatment of **8** with BCl_3 removes the methyl to give diphenol, which is selectively protected as its mono MOM-ether to give **9a**. Alkylation of phenol **9a** with ethyl bromoacetate gives ester **10a**. Hydrolysis of the ester affords acid **11a**. Coupling if the acid **11a**

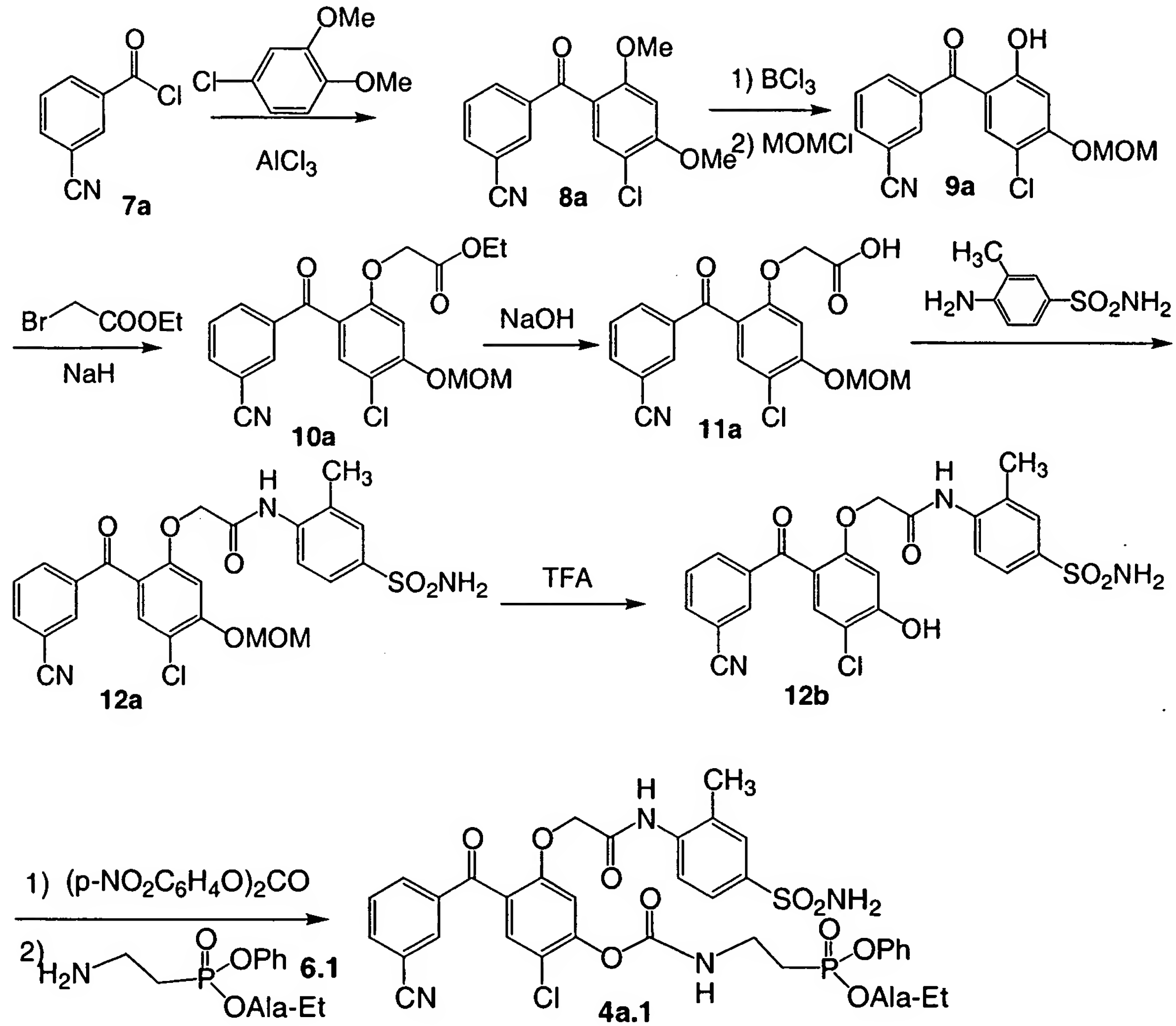
with aniline produces **12a**. The MOM- group is then removed to yield phenol **12b**. Phenol is then activated as its 4-nitro-phenyl carbonate by reacting with bis(4-nitro-phenyl)carbonate, which is subsequently treated with aminoethyl phosphonate to give 4a.1.

Alternatively (Benzophenone Scheme 2), amine 10 is transformed to phenol 11 as described in, the hydroxyl group is then serves as the linking site for a suitable phosphonate group.

Benzophenone Scheme 1



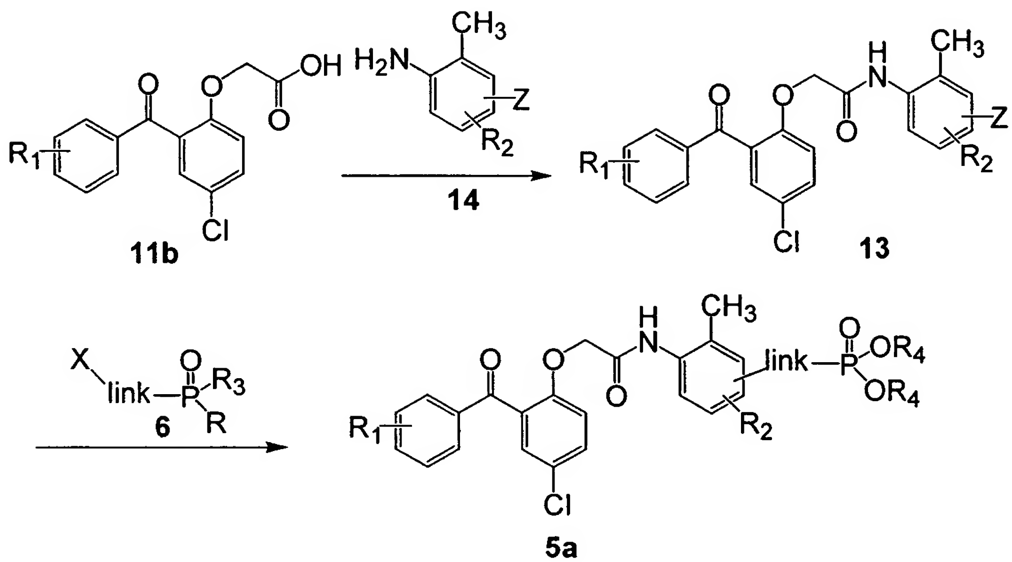
Benzophenone Example 1



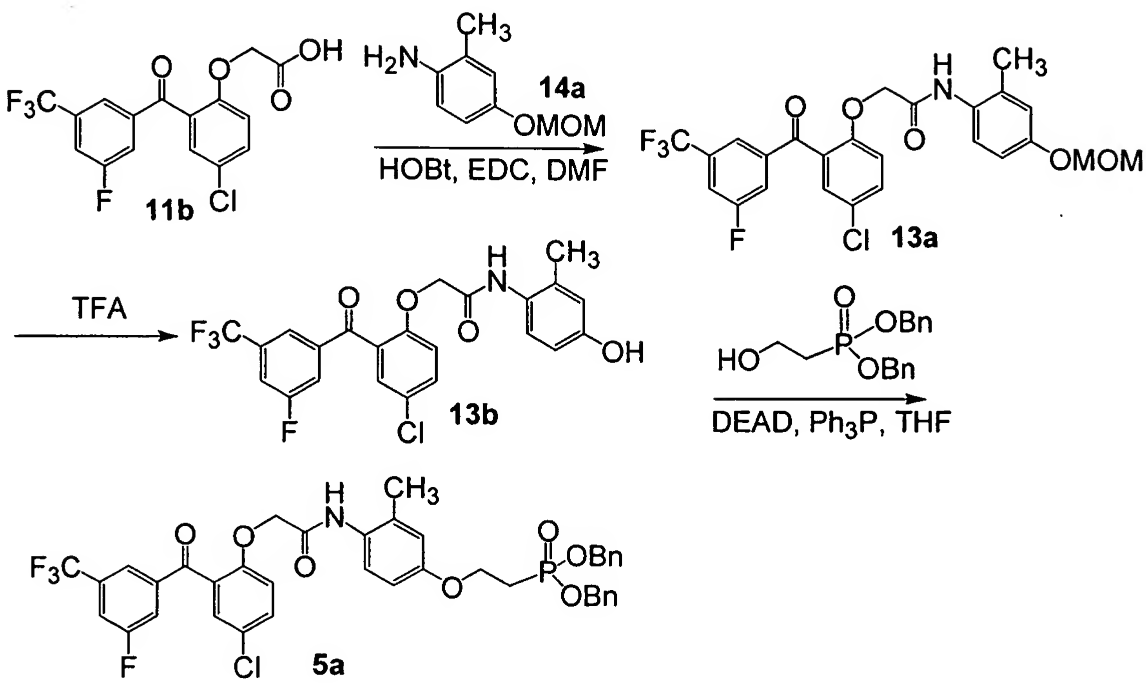
Benzophenone Scheme 2 shows the preparation of phosphonate analog type **5**. Benzophenone **11b** reacts with aniline **14**, bearing a protect hydroxyl or amino group, gives amide **13**. Formation of amide **13** from acid **11b** and aniline **14** is achieved following the standard amide formation methods, many examples are described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2^{nd} Ed. Removal of the protecting group of Z followed by reacting with reagent **6** affords phosphonate analog **5a**. For example (Benzophenone Example 2), acid 11b couples with aniline 14 provides amide 13a. The MOM-group is then deprotected with TFA to afford phenol 13b, which is then coupled with hydroxy ethyl phosphonic acid dibenzyl ester in the presence of Ph3P/DEAD to give phosphonate 5a.

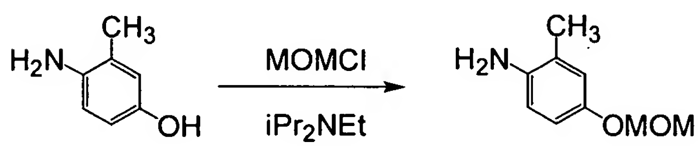
Protected aniline 14a is obtained by treating the commercially available 4-amino-m-cresol with MOMCl in the presence of base, for example Hunig's base.

Benzophenone Scheme 2



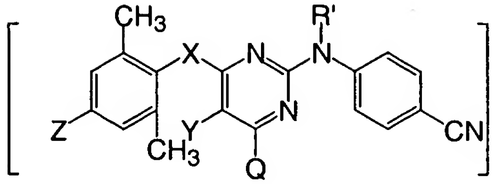
Benzophenone Example 2





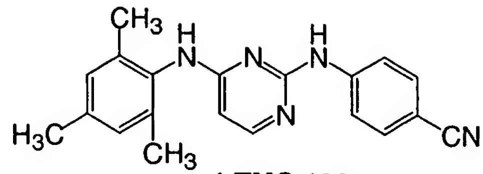
Pyrimidine-like phosphonate NNRTI compounds

The present invention includes Pyrimidine-like phosphonate NNRTI compounds. The present invention also includes methods for the preparation of phosphonate analogs of TMC-125 and TMC-120 class of HIV inhibiting pyrimidines as shown in Pyrimidine Illustration 1 which are potential anti-HIV agents.

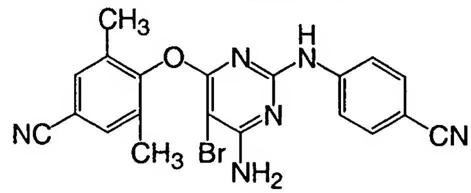


= A

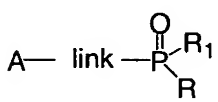
X = NH, O
Y = H, Br, Cl
Z = CN, CH_3
Q = H, NH_2

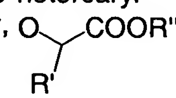


1 TMC-120



2 TMC-125



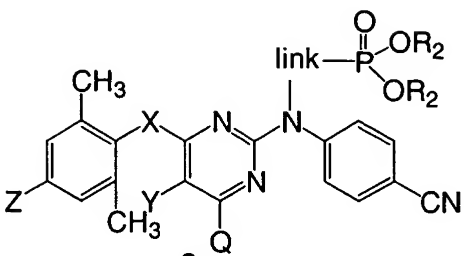
link = linkage group
R = OAr, O-heteroaryl, amino acid ester
substituted OAr, O-heteroaryl
R_1 = amino acid ester, 

Pyrimidine Illustration 1

A link group includes a portion of the structure that links two substructures, one of which is TMC-120 and TMC-125 class of pyrimidines having the general formula shown above, the other is a phosphonate group bearing the appropriate R and R1 groups. The link has at least one uninterrupted chain of atoms other than hydrogen.

TMC-125 and TMC-120 class of pyrimidines have demonstrated to be potent in inhibition of HIV replication. Both TMC-125 and TMC-120 are currently in clinical phase II studies for treatment of HIV infection and AIDs. The present invention provides novel analogs of TMC-120 and TMC-125 class of compound. Such novel TMC-120 and TMC-125 class analogs possess all the utilities of TMC-120 and TMC-125 class and optionally provide cellular accumulation as set forth below.

The intermediate phosphonate esters required for conversion into the prodrug phosphonate moieties bearing amino acid, or lactate esters are shown in Pyrimidine Illustration 2.



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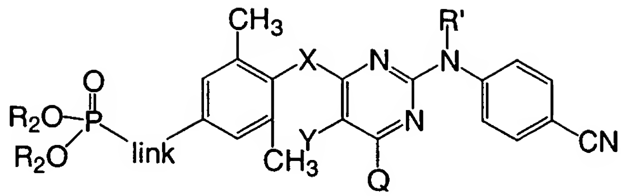

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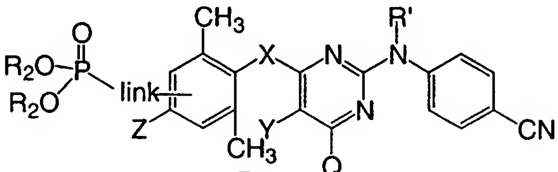

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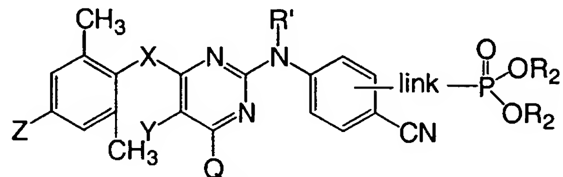

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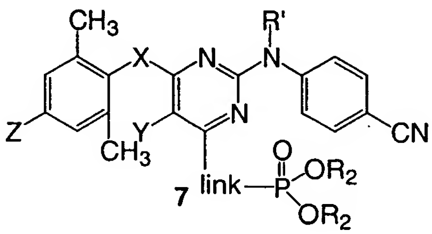

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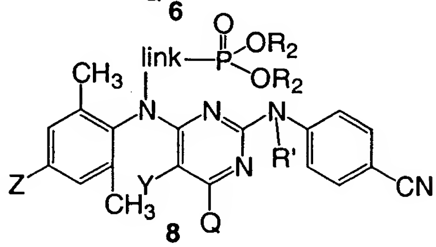

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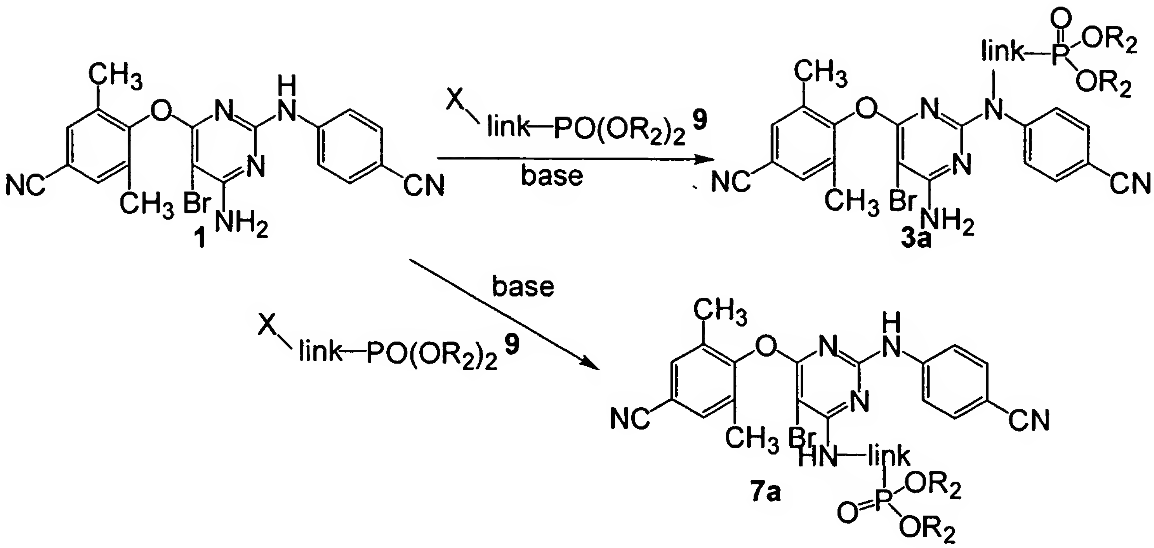
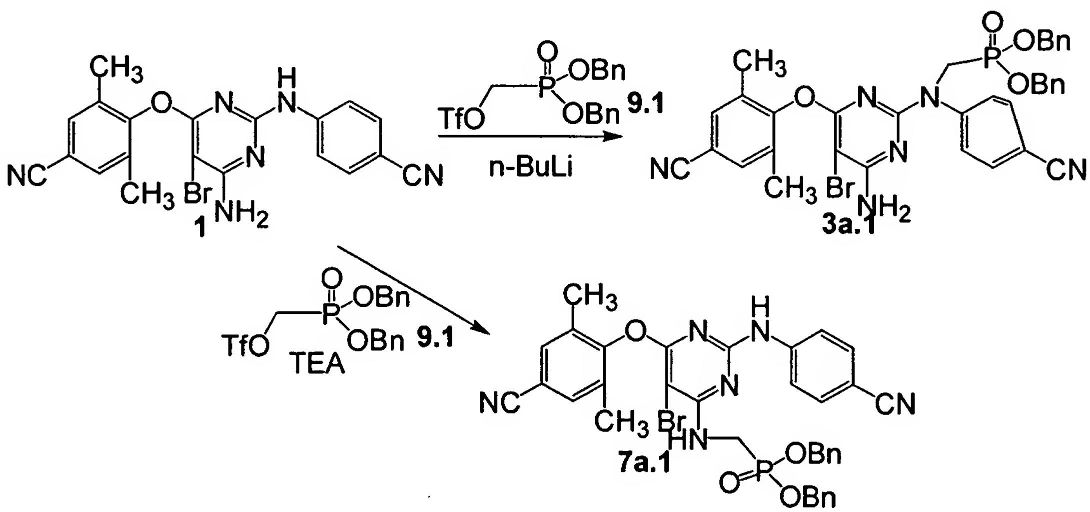
Pyrimidine Illustration 2

Compounds **1** and **2** can be synthesized as described in US Patent No. 6197779 and WO 0027825. Preparation of phosphonate analog **3** and **7** is outlined in Pyrimidine Scheme 1. TMC-125 **1** is dissolved in suitable solvent such as, for example, DMF or other protic solvent, and treated with the phosphonate reagent **9**, bearing a leaving group, such as, for example, bromine, mesyl, tosyl, or trifluoromethanesulfonyl in the presence of a suitable organic or inorganic base, either **3a** or **7a** is obtained as the major product depending on the base. For example, **1** was dissolved in DMF, is treated with n-butyl lithium and 1 equivalent of triflate methyl phosphonic acid dibenzyl ester **9.1** prepared to give phosphonate **3a.1** as the major product. Alternatively, treatment of **1** with **9.1** in acetonitrile in the presence of triethylamine provides **7a.1** as the major product. The above procedure provides phosphonate analog **3** in which the linkage is a methylene group. Using the above procedure but employing different phosphonate reagents **9** in place of **9.1**, the corresponding products **3** and **7** are obtained bearing different linking group.

Pyrimidine Scheme 1

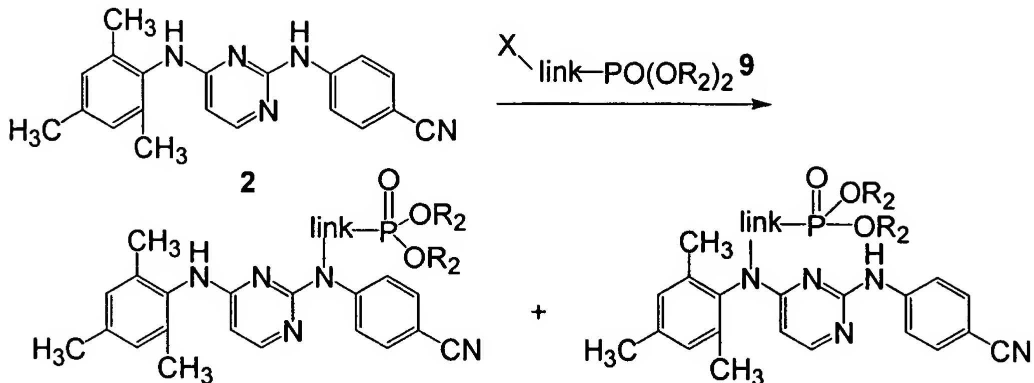


Pyrimidine Example 1



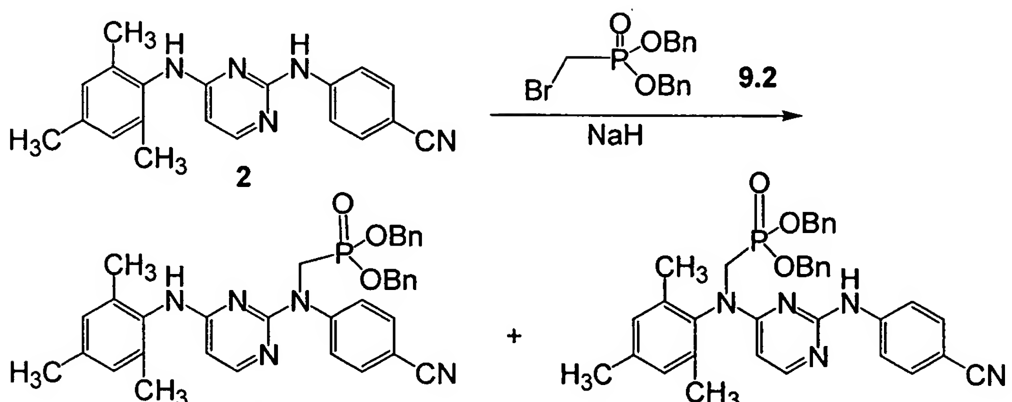
Pyrimidine Scheme 2 shows the preparation of phosphonate conjugates compounds type **3** and **8** in Pyrimidine Illustration 2. TMC-120 **2** is treated with base, and subsequently treated with phosphonate reagent **9** bearing a leaving group, such as, for example, bromine, mesyl, tosyl, or trifluoromethanesulfonyl. The alkylated products are then separated by chromatography. For example (Pyrimidine Example 2), treatment of TMC-120 **2** with NaH in DMF, followed by bromomethyl phosphonic acid dibenzyl ester **9.2** gives phosphonate **3b.1** and **8a.1**. The mixture of phosphonates **3b.1** and **8a.1** is separated by chromatography to give pure **3b.1** and **8a.1**, respectively.

Pyrimidine Scheme 2



2, 3b, 8a

Pyrimidine Example 2

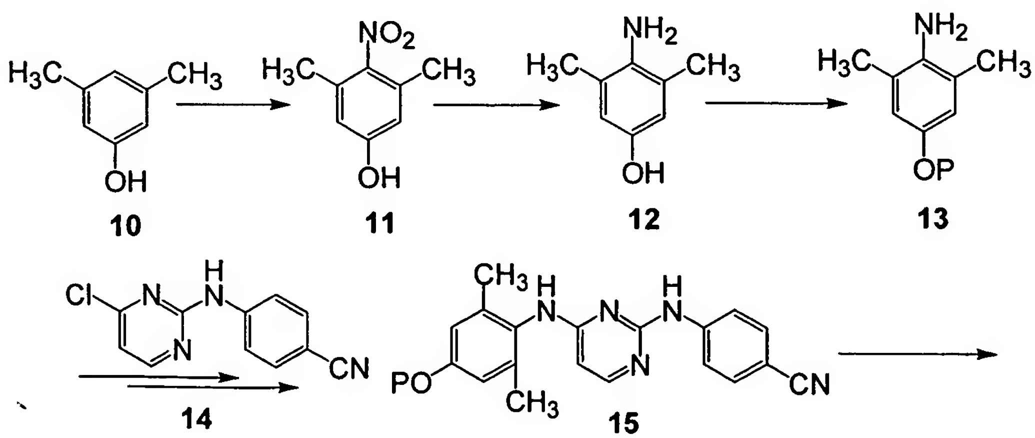


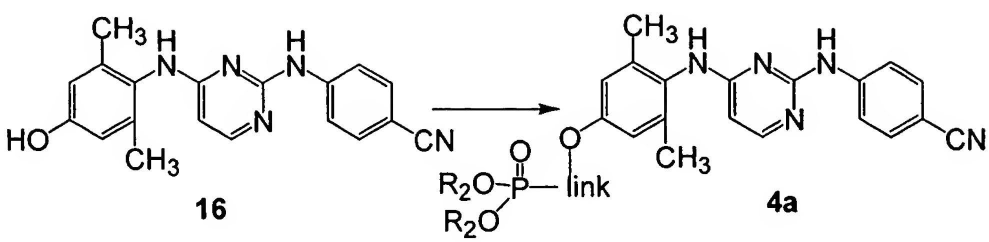
2, 3b.1, 8a.1

Preparation of phosphonate analogs type **4** in Pyrimidine Illustration 2 is shown in Pyrimidine Scheme 3, 4 and 5. Nitration of commercially available 3,5-dimethyl phenol **10** gives **11**, subsequent reduction of the resulting nitrobenzene **11** provide **12**, many examples are described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed. The hydroxyl group of phenol **12** is protected with a suitable protecting group, for example trityl, silyl, benzyl or MOM- etc to give **13** as described in Greene and Wuts, Protecting Groups in Organic Synthesis, 3rd Edition, John Wiley and Sons Inc. Treatment of **14** with **13** following the procedures described in US Patent No. 6197779 and WO 0027825 give **15**. Removal of the protecting group gives phenol **16**. Reaction of phenol **16** with phosphonate reagent **9** in the presence of base in a protic solvent provides **4a**. Nitration (Pyrimidine Scheme 4) of commercially available 2,6-dimethyl phenol provides **18**. Reduction of nitro group to amine,

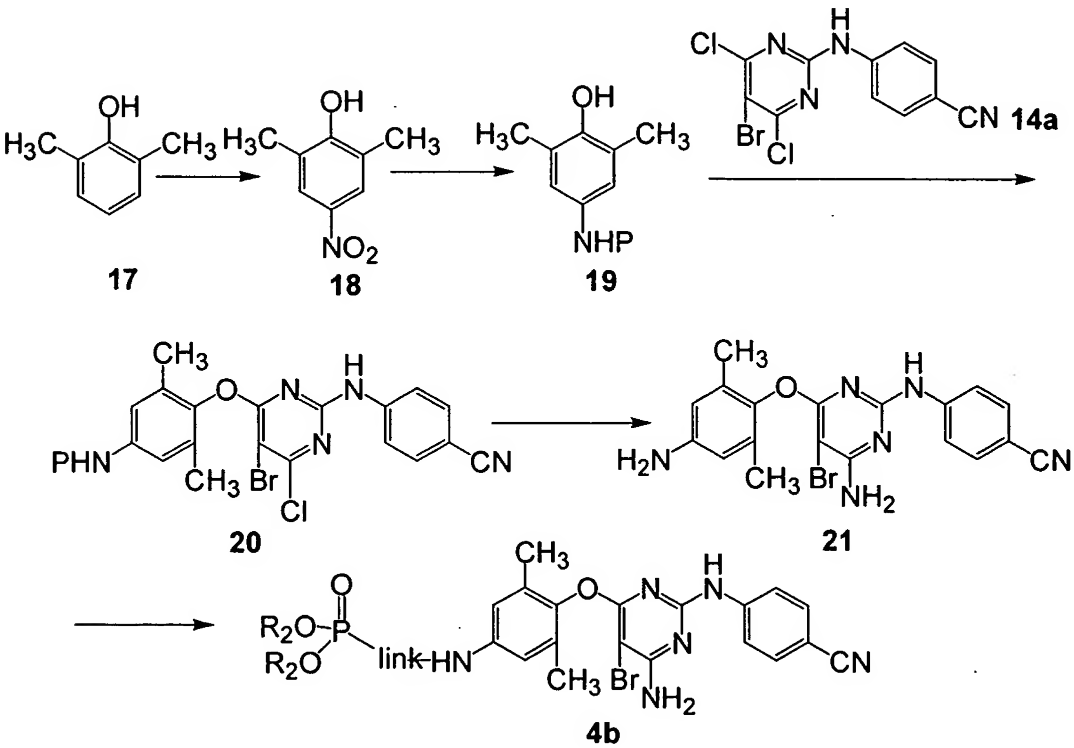
followed by protection of the resultant amine with protecting group, for example, such as trityl, Boc, Cbz etc as described in Greene and Wuts, Protecting Groups in Organic Synthesis, 3rd Edition, John Wiley and Sons Inc. Treatment of **14a** with **19** following the procedures described in US Patent No. 6197779 and WO 0027825 give **20**. Phenol **21** is obtained by treating **20** with NH3 using the procedure described in US Patent No. 6197779 and WO 0027825, followed by removal of the protecting group. Reaction of phenol **21** with phosphonate reagent **9** provides **4b**. As shown in Pyrimidine Scheme 5, the commercially available 2,6-dimethyl-4-cyano-phenol **22** is reduced to benzyl amine, and the resultant amine is protected as described above. Phenol **23** is converted to phosphonate **4c** following the procedure described above for the transformation **19** to **4b**, just replace **19** with **23**. For example (Pyrimidine Example 3), nitration of 2,6-dimethyl phenol with HNO_3 in H_2SO_4 gives phenol **18**. The nitro group is reduced under catalytic hydrogenation condition, and subsequent protection of the resulting amine with Boc- gives phenol **19a**. Treatment of phenol **18** with sodium hydride, followed by reacting the resulting sodium phenoxide with **13** in dioxane provides **20a**. Removal of the Boc- with TFA followed by treatment of the resulting product with NH_3 in isopropyl alcohol according to US Patent No. 6197779 and WO 0027825 replaces the Cl- with NH_2 group to give **21**. The amine group in the phenyl ring is used as attachment site for introduction of phosphonate. Reductive amination of amine with aldehyde **9.3** provides **4b.1**. Treatment of **21** with p-nitro-phenyl carbonate, followed by aminoethyl phosphonate **9.4** affords urea linker **4b.2**.

Pyrimidine Scheme 3

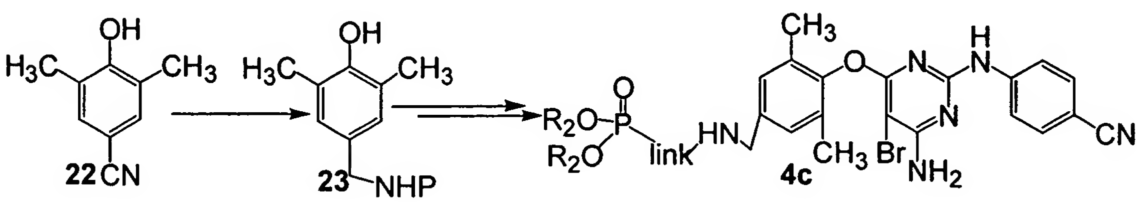




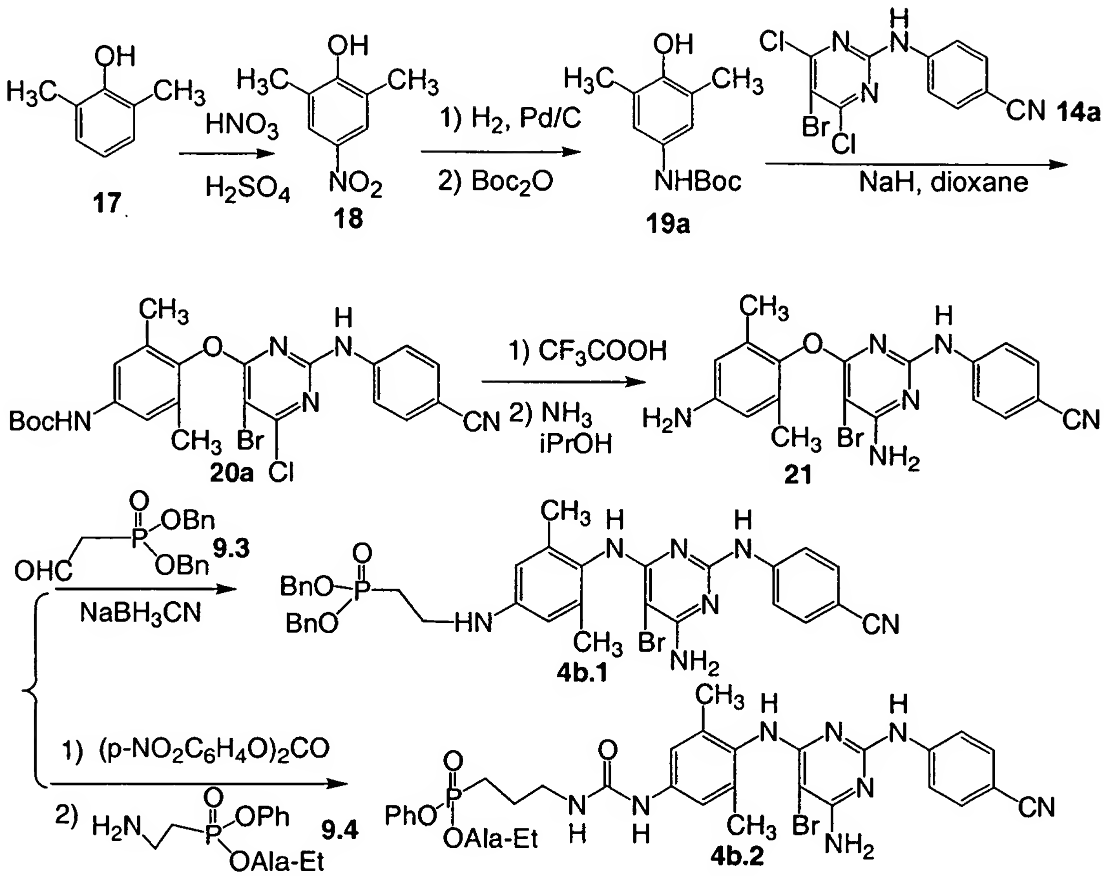
Pyrimidine Scheme 4



Pyrimidine Scheme 5

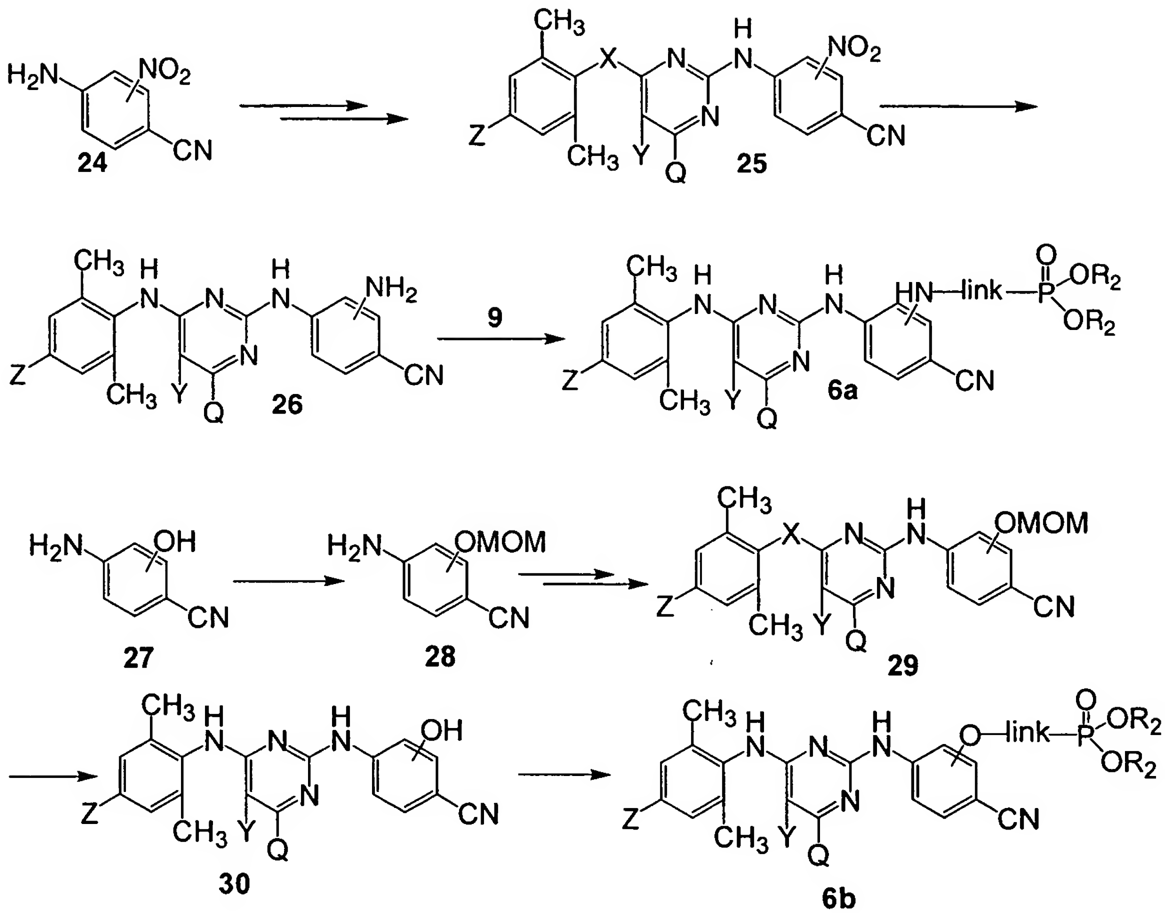


Pyrimidine Example 3

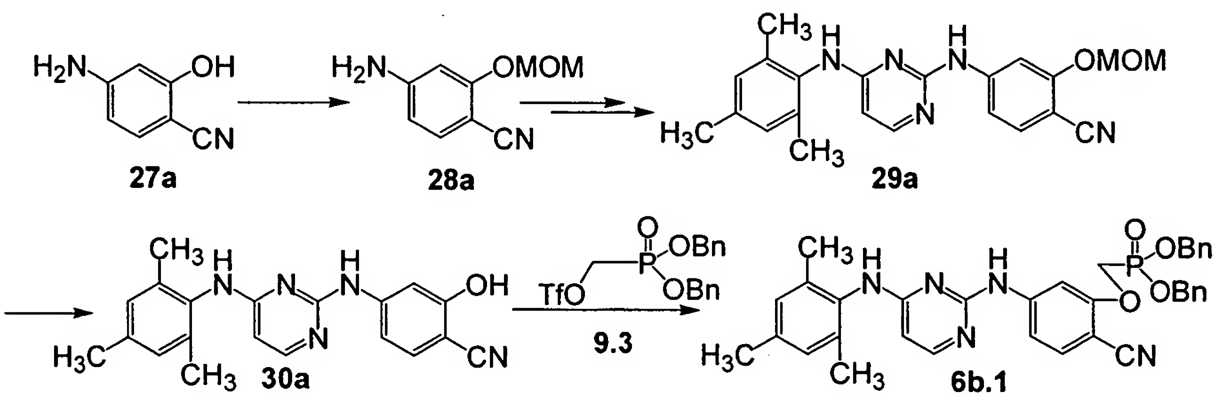


Pyrimidine Scheme 6 shows the preparation of phosphonate type 6 in Pyrimidine Illustration 2. Substituted 4-amino-benzonitriles **24** or **27**, which bearing a protected amino or hydroxyl group, or a precursor of amino group, are used in the replacement of 4-amino-benzonitrile for the preparation of TMC-125 and TMC-120 class of analogs as described in US Patent No. 6197779 and WO 0027825. TMC-120 and TMC-125 analogs **25** and **29** are thus obtained. Removal of protecting group or conversion to amine group from a precursor, such as a nitro group, provide **26** or **30**, respectively. Treatment of **26** and/or **30** with reagent **9** yield **6a** and/or **6b** respectively. For example (Pyrimidine Example 4), the hydroxyl group of 4-amino-2-hyroxy-benzonitrile **27a** is protected as its MOM-ether to give **28a**. Following the procedure in US Patent No. 6197779 and WO 0027825, **28a** is converted to TMC-120 analog **29a**. Removal of MOM-ether with TFA provides phenol **30a**, which is treated with trifluoromethylsulfonyl phosphonic acid benzyl ester together with Cs_2CO_3 in acetonitrile affords phosphonate analog **6b.1**.

Pyrimidine Scheme 6



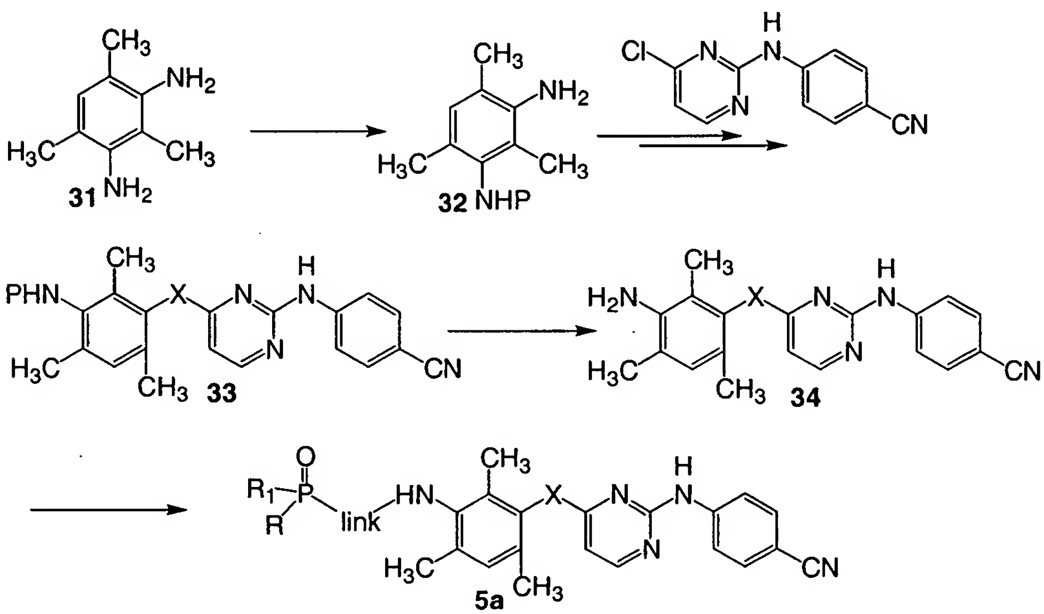
Pyrimidine Example 4



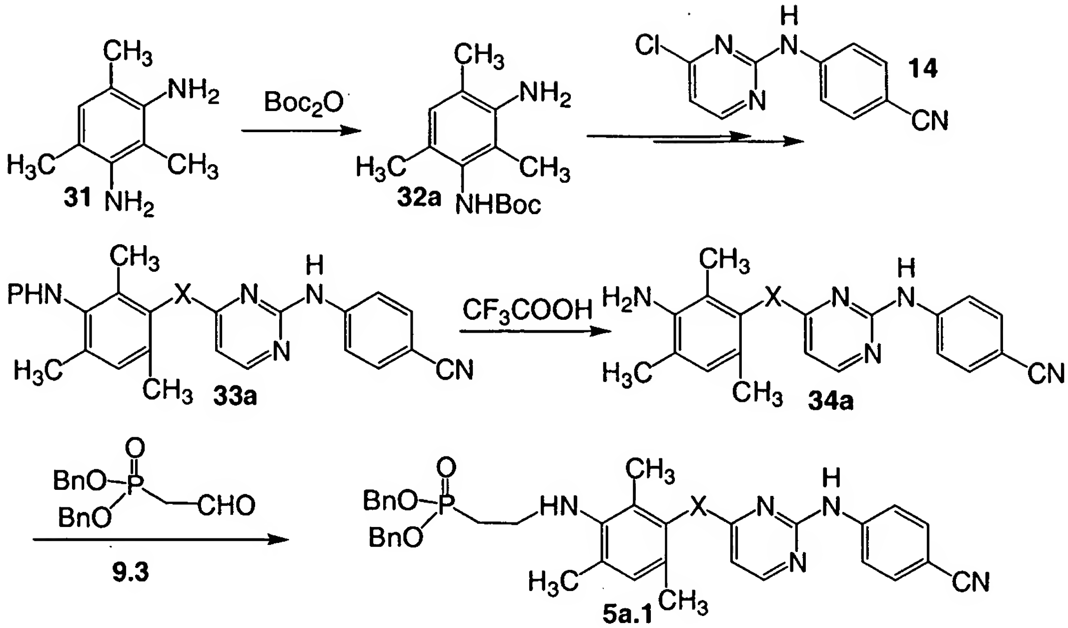
Preparation of phosphonate analog type 5 in Pyrimidine Illustration 2 is shown in Pyrimidine Scheme 7. Substituted aniline, which bearing a protected amino or hydroxyl group, is converted to TMC-120 or TMC-125 analogs following the procedures described in US Patent

No. 6197779 and WO 0027825. Removal of the protecting group gives analog **34**. The amino or hydroxyl group in **33** serves as attachment site for introduction of phosphonate. Reaction of **33** with reagent **9** provides **5a**. For example (Pyrimidine Example 5), commercially available 2-amino-2,4,6-trimethyl-aniline is selectively protected as Boc- carbamate. Reaction of **32a** with **13** provides **33a**. Removal of Boc with TFA affords aniline **34a**. Reductive amination with reagent 9.2 yields phosphonate analog **5a.1**.

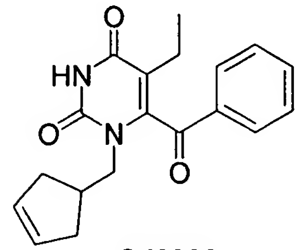
Pyrimidine Scheme 7



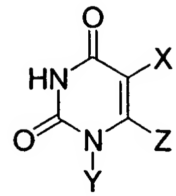
Pyrimidine Example 6



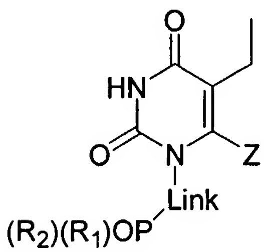
SJ3366-like phosphonate NNRTI compounds



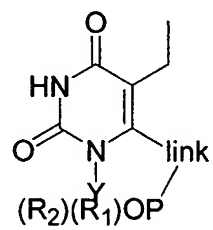
SJ3366



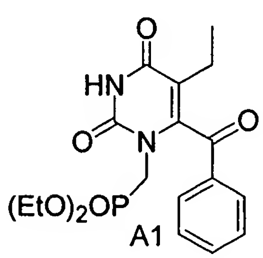
X = alkyl C_1-C_{12}branched or straight
Y = alkyl, alkoxy, with or without link-$PO(R_1)(R_2)$
Z= Y_2-link-$PO(R_1)(R_2)$ or
Y_2-Aryl (optionally substituted)
or Y_2-alkyl
Y_2=CR_2, O, S, NR (R = H, alkyl C_1-C_{12}), C=O, COH

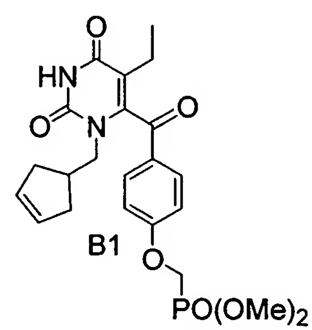


Type A [Y = link $PO(R_1)(R_2)$]



Type B [Z=link $PO(R_1)(R_2)$]





SJ3366 is described in US Patent No. 5922727. The present invention provides novel phosphonate analogs of SJ3366 which possess all the utilities of SJ3366 and optionally provide cellular accumulation as set forth below.

The present invention also relates to the delivery of SJ3366-like phosphonate compounds which are optionally targeted for site-specific accumulation in cells, tissues or organs. More particularly, this invention relates to analogs of SJ3366 which comprise SJ3366 linked to a $PO(R_1)(R_2)$ moiety.

SJ3366 may be covalently bonded directly or indirectly by a link to the $PO(R_1)(R_2)$ moiety. An R group of the $PO(R_1)(R_2)$ moiety can possibly be cleaved within the desired delivery site, thereby forming an ionic species which does not exit the cell easily. This may cause accumulation within the cell and can optionally protect the SJ3366 analog from exposure to metabolic enzymes which would metabolize the analog if not protected within the cell. The cleavage may occur as a result of normal displacement by cellular nucleophiles or enzymatic action, but is preferably caused to occur selectively at a predetermined release site. The advantage of this method is that the SJ3366 analog may optionally be delivered site-specifically, may optionally accumulate within the cell and may optionally be shielded from metabolic enzymes.

The following examples illustrate various aspects of the present invention and are not to be construed to limit the types of analogs that may employ this strategy of linking SJ3366 or an SJ3366 analog to a $PO(R_1)(R_2)$ moiety in any manner whatsoever.

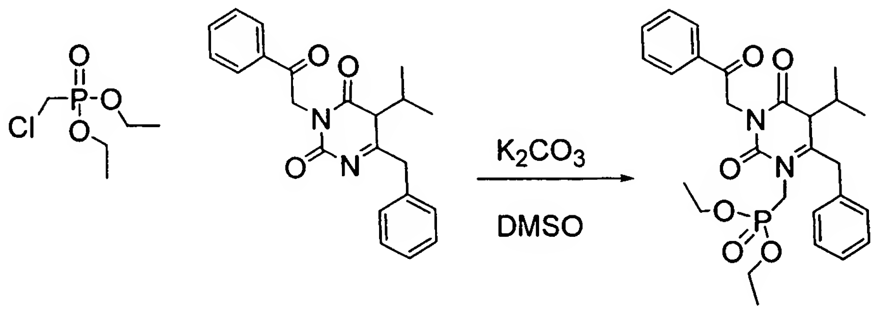
Preparation of compounds of type A require a link which can react with SJ3366 or an intermediate or analog thereof, to result in a covalent bond between the link and the drug-like compound. The link is also attached to the phosphorous containing moiety as shown in an example of type A, namely A1.

Examples of type A can be made by 1-alkylation of the 3-phenacyl derivatives 35 and 36 (synthesis described in *J. Med. Chem.* 1995, 38, 1860-2865, and so numbered 35 and 36 therein) with alkyl halide containing links followed by deprotection of the 3-phenacyl group.

An example synthesis is as follows, and is shown in SJ3366 Scheme 1. 6-Benzyl-5-isopropyl-3-(2-phenyl-allyl)-dihydro-pyrimidine-2,4-dione, as prepared in *J. Med. Chem.* 1995, 38, 15, 2860-2865, is treated analogously to the reference article authors' treatment in preparing their compounds 37-40, but in the case of compound A1, commercially available chloromethyldiethylphosphonate is used as the alkylating agent. Alternatively the link is connected by starting with the same drug-like compound and using a triflated link. The triflated link is prepared, for example, by reaction of allyl bromide with dibenzylphosphite and potassium carbonate in acetonitrile at 65°C. Ozonolysis of the double bond followed by treatment with sodium borohydride would provide the alcohol, which could then be reacted with triflic anhydride with 2,6 lutidine in dichloromethane to produce the triflate. The triflated material could then be attached by stirring it with, for example 6-Benzyl-5-isopropyl-3-(2-phenyl-allyl)-

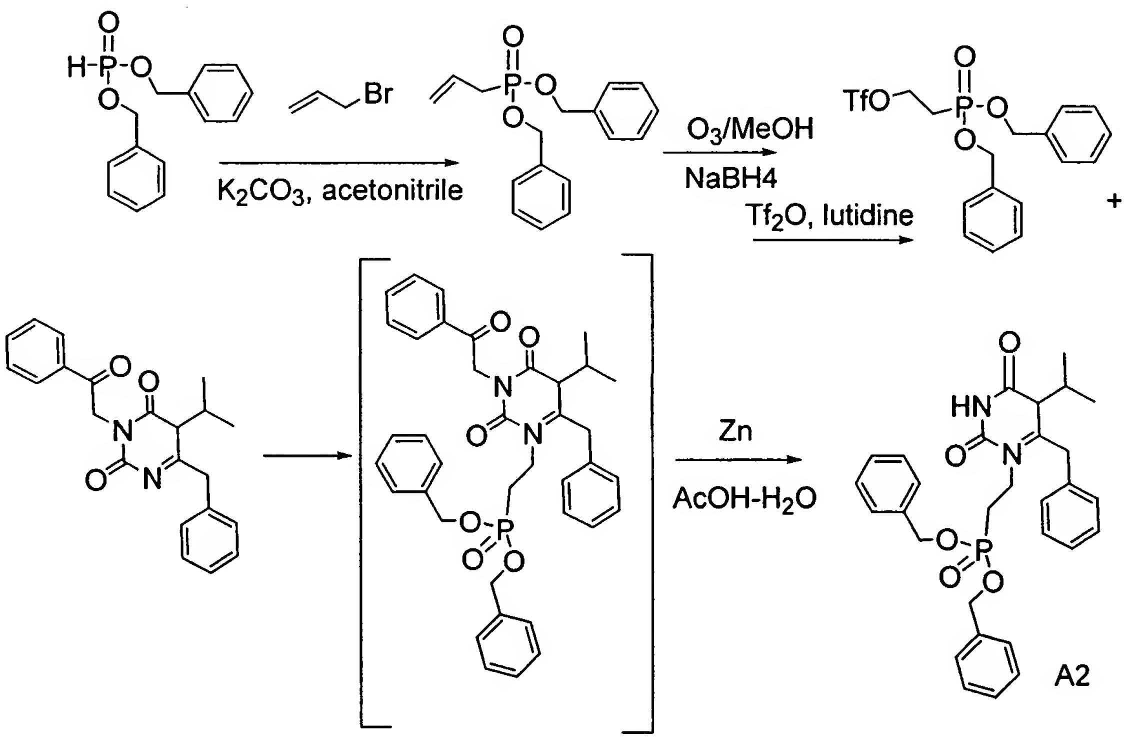
dihydro-pyrimidine-2,4-dione with 2,6 lutidine or other base in an appropriate solvent such as acetone. This procedure will provide examples A1 and A2.

SJ3366 Scheme 1



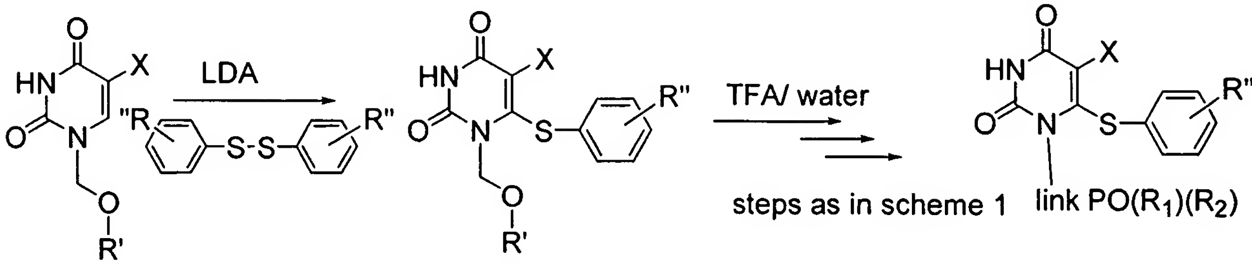
6-Benzyl-5-isopropyl-3-(2-oxo-2-phenyl-ethyl)
-5*H*-pyrimidine-2,4-dione

A1



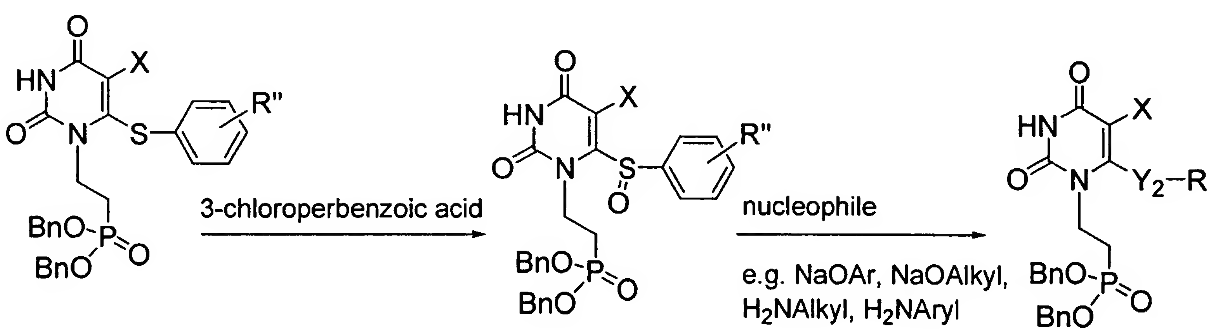
SJ3366 Scheme 1 can be extended to include analogs with various moieties at C6 in addition to substituted benzyl rings. For example, the LDA treatment described in *J. Med. Chem.* 1995, 38, 15, 2860-2865 followed by disulfide addition provides intermediates which can then be treated similarly to those in SJ3366 Scheme 1 to install the link $PO(R_1)(R_2)$ at the 1 position.

SJ3366 Scheme 2



SJ3366 Scheme 3 also demonstrates a method to prepare analogs with oxygen or nitrogen at Y_2 attached to the 6 position. This method is explained fully in *J. Med. Chem.* 1991, 34,1, 349 - 357. Using this method allows for aryl and alkyl groups to be attached to the 6 position by either oxygen or nitrogen. A specific example is shown in the bottom row of the boxes in SJ3366 Scheme 7 below.

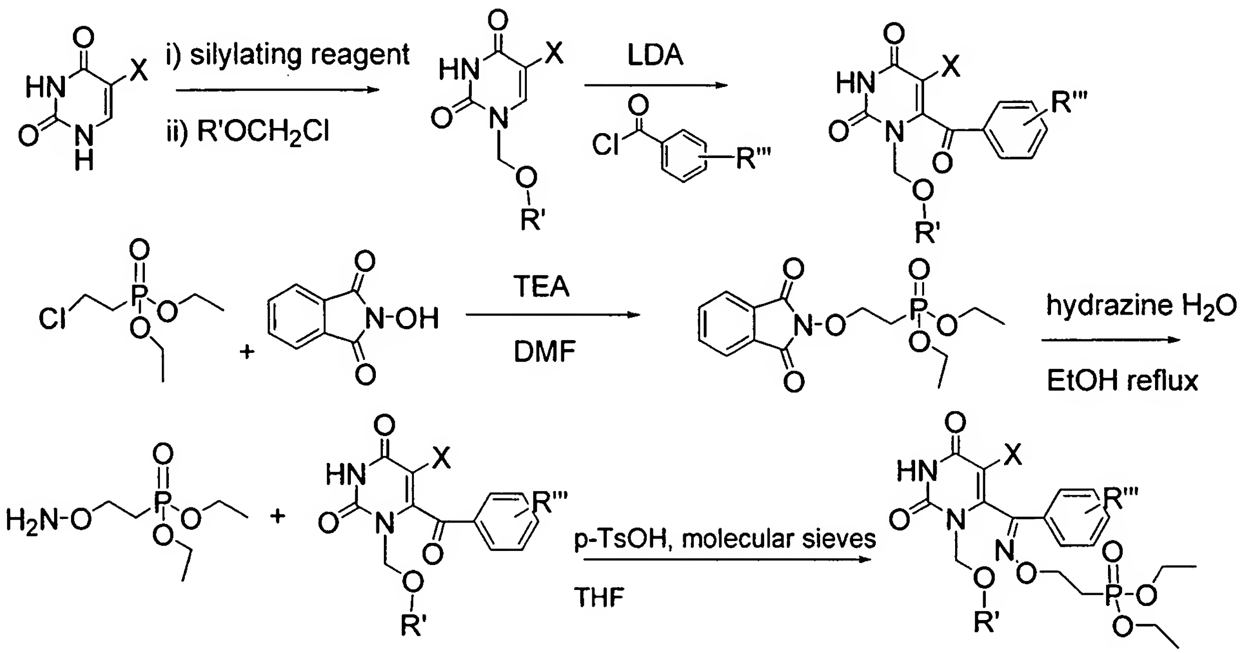
SJ3366 Scheme 3



Alternatively the 5 position may be functionalized after the nucleophile is appended by the TFA/water deprotection and alkylation strategy shown in SJ3366 Scheme 2. Analogs with methylene, a secondary alcohol or a ketone at the 6 position are readily prepared following the LDA procedure in SJ3366 Scheme 2, but using substituted or unsubstituted PhCOCl in place of a disulfide, as is done in *J. Med. Chem.* 1991, 34, 1 page 351. The resultant ketone can be converted to an oxime ether (SJ3366 Scheme 4), an ether (SJ3366 Scheme 5) or reduced to a methylene (SJ3366 Scheme 6). SJ3366 Scheme 6 can be extended with the deprotection and alkylation steps described in SJ3366 Scheme 2. The methylene, secondary alcohol and ether are

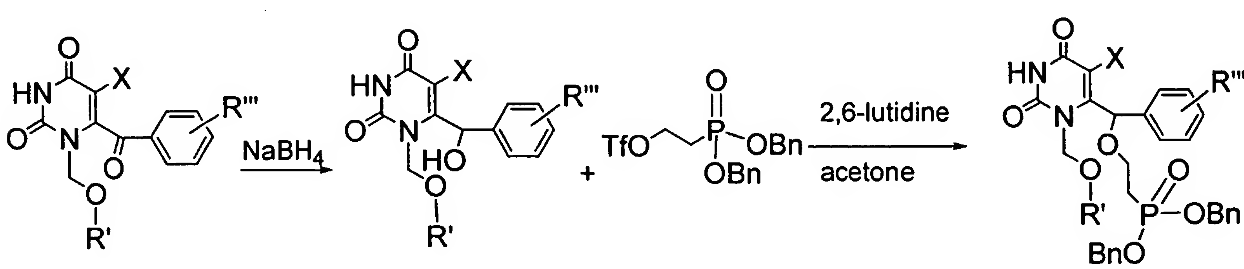
all described in *J. Med. Chem.* 1991, 34, 1 page 349-357, and the oxime ether can be prepared as described below (SJ3366 Scheme 4).

SJ3366 Scheme 4

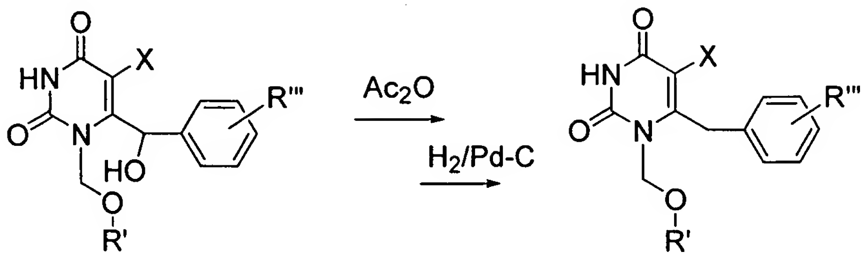


Alternatively the ketone containing compound could undergo deprotection at the 1 position and attachment of the link $PO(R_1)(R_2)$ as in SJ3366 Scheme 2 above.

SJ3366 Scheme 5

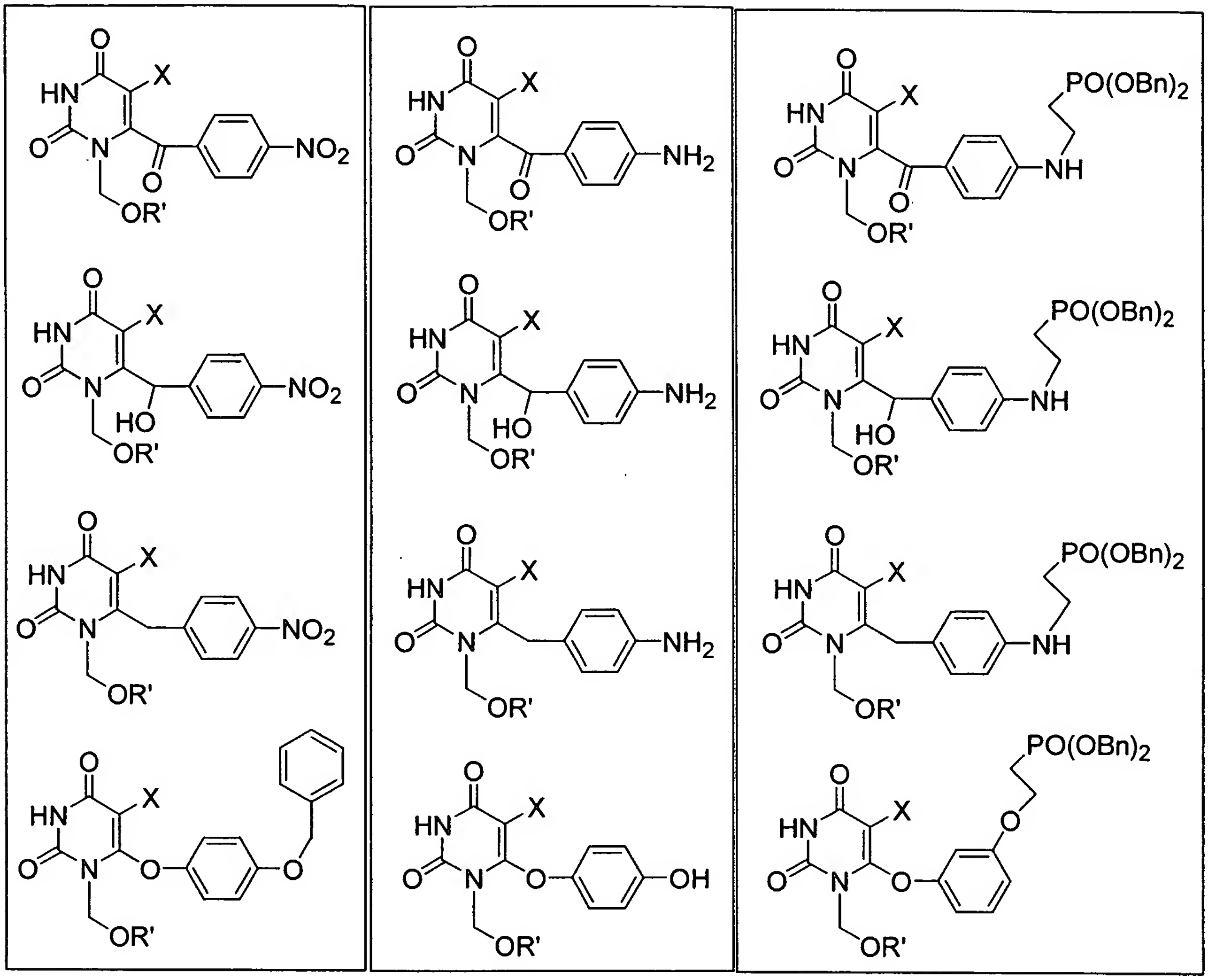


SJ3366 Scheme 6

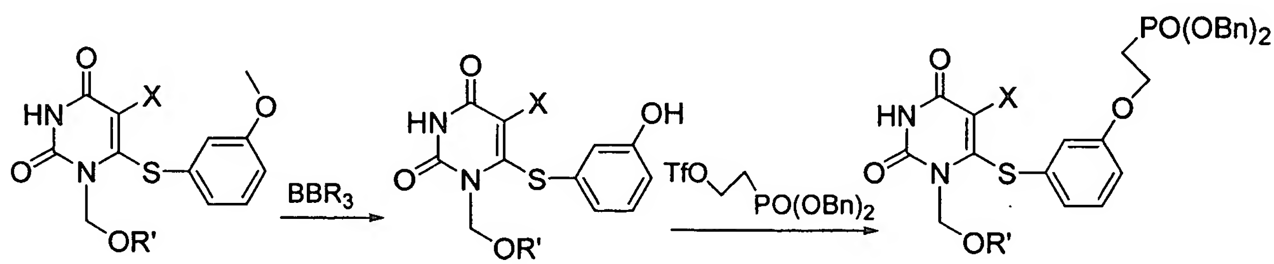


The above shown compounds could also have a reactive group at the aryl or alkyl substituent on the 5 or the 6 position that would allow for attachment of the $PO(R_1)(R_2)$ group. These reactive groups are protected by a protecting group, or be present in the form of a masked functionality, such as the manner in which a nitro group would mask an amine. SJ3366 Scheme 7 shows some more representative examples of the many ways an attachment of a $PO(R_1)(R_2)$ is made. The chemistry involved is explained above, except for the BBr3 demethylation, which is a common procedure (J.F.W.McOmie and D.E. West, Org. Synth. Collect. Vol. V, 412, (1973) for demethylating methoxyaryl rings. The compounds in box A are treated with hydrogen gas and stirred in a solvent such as ethanol or methanol with a suspension of 10% palladium on carbon. The anilines or alcohols are then treated with a triflated $PO(R_1)(R_2)$ containing group as described above.

SJ3366 Scheme 7



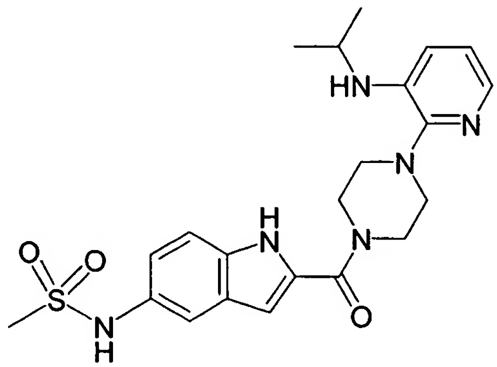
A B C



Delavirdine-like phosphonate NNRTI compounds

Diaromatic compounds refer to any diaromatic substituted compound, more specifically, bis(heteroaryl) piperazine (BHAP), more specifically 1{5-methanesulfonamidoindolyl-2-

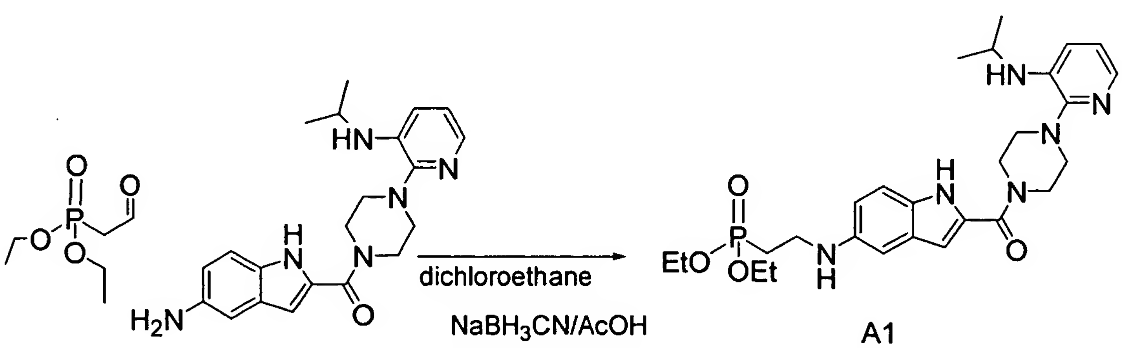
carbonyl}-4-{3-(1-methylethylamino)-2-pyridinyl}piperazine as found in US Patent No. 5563142 claim 8 column 90 line 49-51, and pharmaceutically acceptable salts thereof.



Delavirdine

Preparation of compounds of type A, B, and C require a link which can react with a drug-like compound which is either 1{5-methanesulfonamidoindolyl-2-carbonyl}-4-{3-(1-methylethylamino)-2-pyridinyl}piperazine or an intermediate thereof, to result in a covalent bond between the link and the drug-like compound. The link is also attached to the phosphorous containing moiety shown in examples of type A, B and C, namely A1, B1 and C1.

Delavirdine Scheme 1



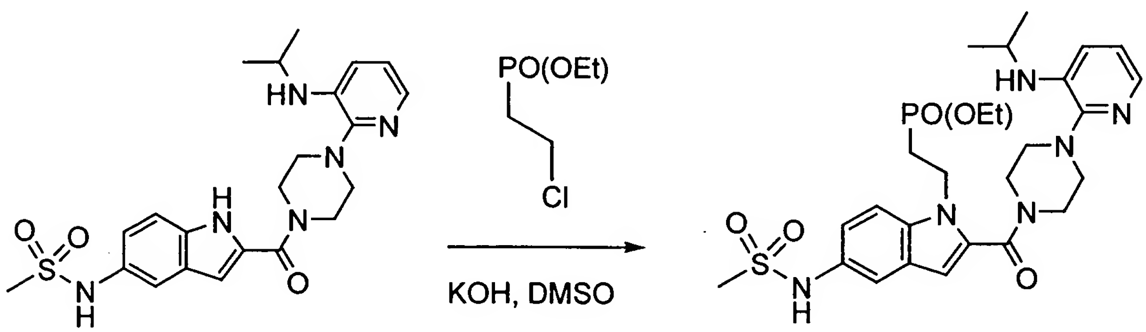
Examples of type A can be made by reacting the aminoindole NH_2 of the immediate precursor to delavirdine (1-[5-amidoindolyl-2-carbonyl]-4-[3-(1-methylethylamino)-2-pyridinyl]piperazine, such as example 101 in US Patent No. 5563142, synthesis described therein, with the phosphorous containing moiety having an aldehyde as the reactive part of the link. The aldehyde and NH_2 group react through a reductive amination reaction, which can be

performed by stirring both reagents in, for example dichloroethane, for approximately two hours and then adding acetic acid and sodium cyanoborohydride, or by other standard methods known to most organic chemists. Commercially available aldehyde containing phosphonates such as that shown in the below Delavirdine Scheme 1 can be used to prepare example A1.

This method may be extended to synthesize molecules with the link attached at other positions on the indole phenyl ring by following the procedures described in US Patent No. 5563142 but substituting starting materials as relevant to obtain the indole with the desired substitution pattern.

Examples of type B can be prepared by reacting the indole NH of delavirdine with, for example, a link which contains an alkyl chloride in the presence of KOH in DMSO as described in *J. Med. Chem.* 34, 3, 1991, 1099-1110. The alkyl chloride link is for example commercially available chloromethyl diethoxyphosphonate, giving example B1.

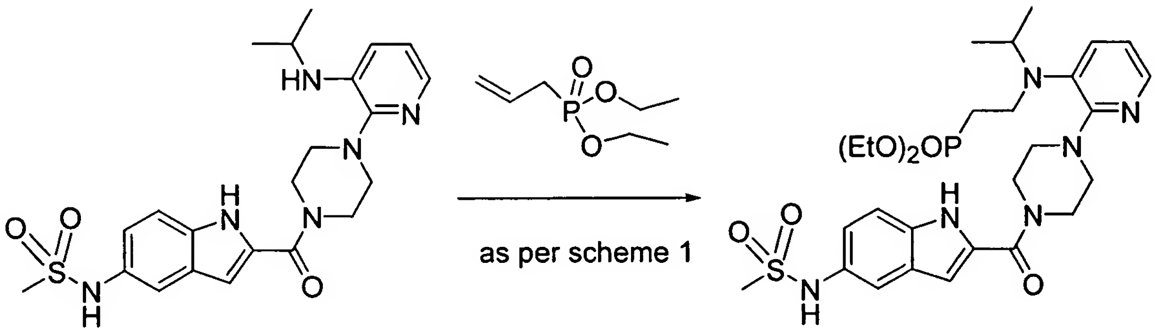
Delavirdine Scheme 2



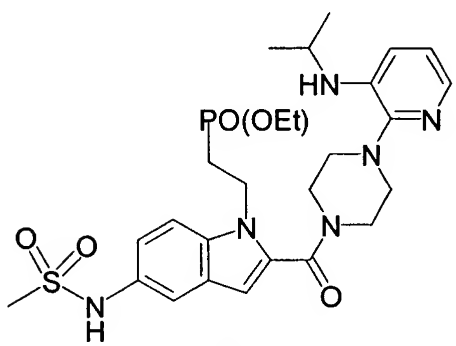
B1

Examples of type C can be made by reacting the secondary amine of delavirdine with the phosphorous containing moiety having an aldehyde as the reactive part of the link. The aldehyde and NH group react through a reductive amination reaction, which can be performed by stirring both reagents in, for example dichloroethane, for approximately two hours and then adding acetic acid and sodium cyanoborohydride, or by other standard methods known to most organic chemists. In this example the aldehyde containing phosphonate is commercially available. This procedure will provide example C1.

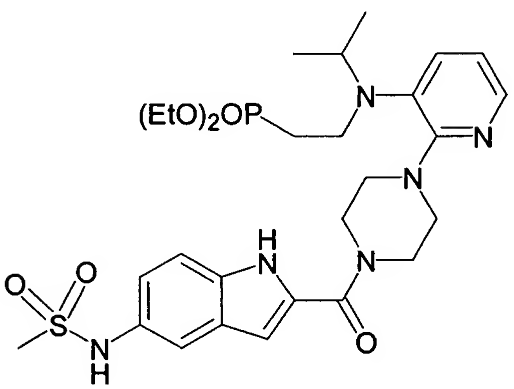
Delavirdine Scheme 3



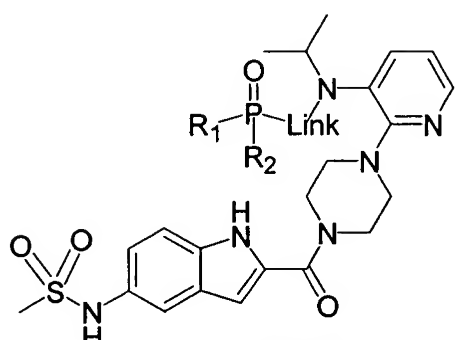
C1



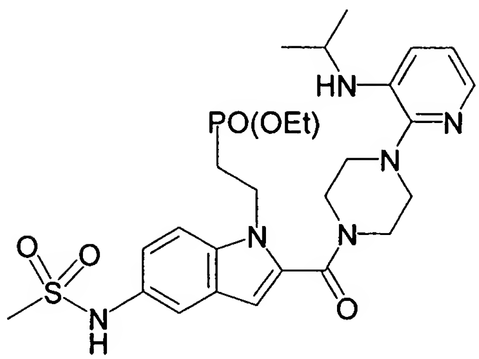
B1



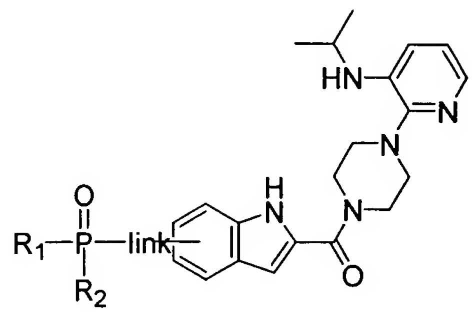
C1



Type C



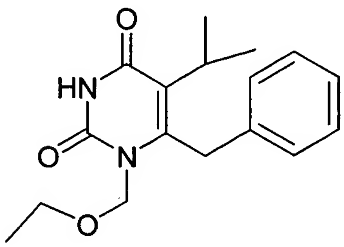
Type B

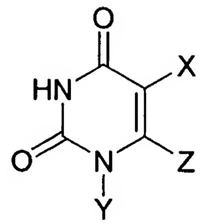


Type A

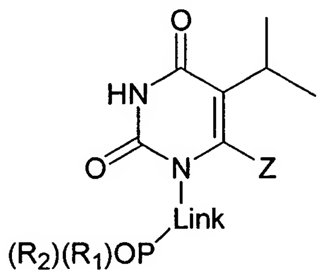
The present invention provides novel analogs of 1{5-methanesulfonamidoindolyl-2-carbonyl}-4-{3-(1-methylethylamino)-2-pyridinyl}piperazine. Such novel 1{5-methanesulfonamidoindolyl-2-carbonyl}-4-{3-(1-methylethylamino)-2-pyridinyl}piperazine analogs possess all the utilities of 1{5-methanesulfonamidoindolyl-2-carbonyl}-4-{3-(1-methylethylamino)-2-pyridinyl}piperazine and optionally provide cellular accumulation as set forth below.

Emivirine-like phosphonate NNRTI compounds

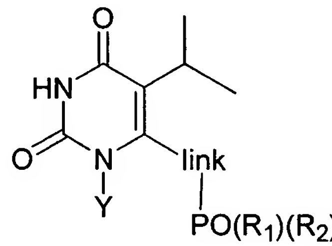




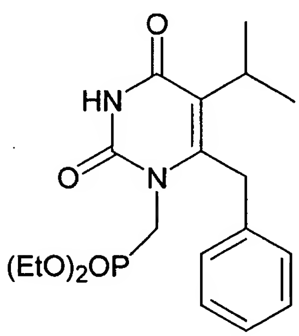
X = alkyl C_1-C_{12}branched or straight
Y = alkyl, alkoxy, with or without link-PO(R_1)(R_2)
Z= Y^2-link-PO(R_1)(R_2) or
Y^2-Aryl (optionally substituted)
or Y^2-alkyl
Y^2=CR_2, O, S, NR (R = H, alkyl C_1-C_{12}), C=O, COH



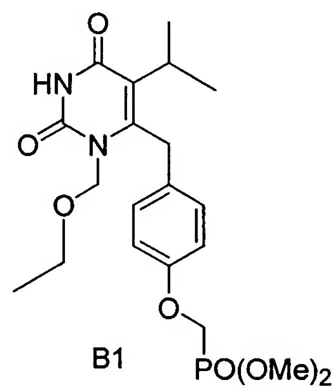
Type A [Y = link PO(R_1)(R_2)]



Type B [Z=link PO(R_1)(R_2)]



A1



B1

The present invention provides novel phosphonate analogs of Emivirine and pharmaceutically acceptable salts thereof. Emivirine is described in US Patent No. 5461060. Such novel Emivirine analogs possess all the utilities of Emivirine and optionally provide cellular accumulation as set forth below.

The present invention also relates to the delivery of Emivirine-like phosphonate compounds which are optionally targeted for site-specific accumulation in cells, tissues or organs. More particularly, this invention relates to analogs of Emivirine which comprise Emivirine linked to a $PO(R_1)(R_2)$ moiety.

Emivirine is covalently bonded directly or indirectly by a link to the $PO(R_1)(R_2)$ moiety. An R group of the $PO(R_1)(R_2)$ moiety can possibly be cleaved within the desired delivery site, thereby forming an ionic species which does not exit the cell easily. This may cause accumulation within the cell and can optionally protect the Emivirine analog from exposure to metabolic enzymes which would metabolize the analog if not protected within the cell. The cleavage may occur as a result of normal displacement by cellular nucleophiles or enzymatic action, but is preferably caused to occur selectively at a predetermined release site. The advantage of this method is that the Emivirine analog may optionally be delivered site-specifically, may optionally accumulate within the cell and may optionally be shielded from metabolic enzymes.

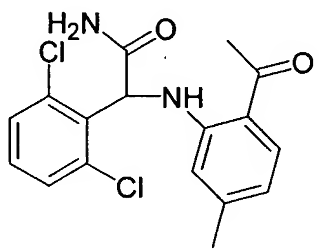
Link: an atom or molecule which covalently binds together two components. In the present invention, a link is intended to include atoms and molecules which can be used to covalently bind Emivirine or an analog thereof at one end of the link to the $PO(R_1)(R_2)$ at the other end of the link. The link must not prevent the binding of the analog with its appropriate receptor. Examples of suitable links include, but are not limited to, polymethylene [$-(CH_2)_n$, where n is 1-10], ester, amine, carbonate, carbamate, ether, olefin, aromatic ring, acetal , heteroatom containing ring, or any combination of two or more of these units. The $PO(R_1)(R_2)$ may also be directly attached. A skilled artisan will readily recognize other links which can be used in accordance with the present invention.

The preceding SJ3366 Schemes 1-7 for SJ3366-like phosphonate NNRTI compounds illustrate various aspects of the present invention and are not to be construed to limit the types of analogs that may employ this strategy of linking Emivirine or an Emivirine analog to a $PO(R_1)(R_2)$ moiety in any manner whatsoever.

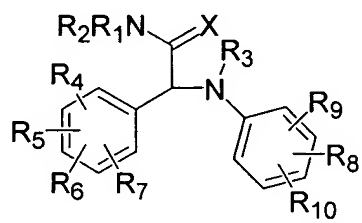
Loviride-like phosphonate NNRTI compounds

The present invention relates to Loviride-like phosphonate NNRTI compounds and their delivery to cells, tissue or organs which are optionally targeted for site-specific accumulation. More particularly, this invention relates to phosphonate analogs of Loviride, and their pharmaceutically acceptable salts and formulations, which comprise Loviride linked to a phosphonate, *i.e.* $PO(R_1)(R_2)$ moiety.

The groups R_1-R_{10} are as described in US Patent No. 5556886, and also can be link $PO(R_1)(R_2)$. The present invention provides novel phosphonate analogs of Loviride. Such novel Loviride analogs possess all the utilities of NNRTI properties as Loviride and optionally provide cellular accumulation as set forth below.



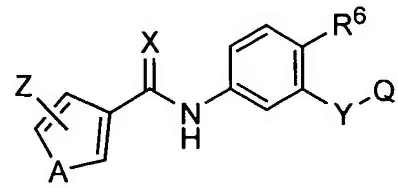
Loviride



Loviride may be covalently bonded directly or indirectly by a link to the $PO(R_1)(R_2)$ moiety. An R group of the $PO(R_1)(R_2)$ moiety can possibly be cleaved within the desired delivery site, thereby forming an ionic species which does not exit the cell easily. This may cause accumulation within the cell and can optionally protect the Loviride analog from exposure to metabolic enzymes which would metabolize the analog if not charged or protected within the cell. The cleavage may occur as a result of normal displacement by cellular nucleophiles or enzymatic action, but is preferably caused to occur selectively at a predetermined release site. The advantage of this method is that the Loviride analog may optionally be delivered site-specifically, may optionally accumulate within the cell and may optionally be shielded from metabolic enzymes.

The following examples illustrate various aspects of the present invention and are not to be construed to limit the types of analogs that may employ this strategy of linking Loviride or an Loviride analog to a $PO(R_1)(R_2)$ moiety in any manner whatsoever.

UC781-like phosphonate NNRTI compounds



The present invention includes UC781-like phosphonate compounds and pharmaceutically acceptable salts thereof. UC781 is described in US Patent No. 6143780.

A, X, Y, Q and R^6 in the formula above are as defined in US Patent No. 6143780. Z represents any substitution of the heteroatom ring. Also the heteroatom ring may be six membered. The present invention provides novel phosphonate analogs of UC781. Such novel UC781 analogs possess all the utilities of UC781 and optionally provide cellular accumulation as set forth below. The present invention also relates to the delivery of UC781- like phosphonate compounds which are optionally targeted for site-specific accumulation in cells, tissues or organs. More particularly, this invention relates to analogs of UC781 which comprise UC781 linked to a $PO(R_1)(R_2)$ moiety.

UC781 is covalently bonded directly or indirectly by a link to the $PO(R_1)(R_2)$ moiety. An R group of the $PO(R_1)(R_2)$ moiety can possibly be cleaved within the desired delivery site, thereby forming an ionic species which does not exit the cell easily. This may cause accumulation within the cell and can optionally protect the UC781 analog from exposure to metabolic enzymes which would metabolize the analog if not protected within the cell. The cleavage may occur as a result of normal displacement by cellular nucleophiles or enzymatic action, but is preferably caused to occur selectively at a predetermined release site. The advantage of this method is that the UC781 analog may optionally be delivered site-specifically, may optionally accumulate within the cell and may optionally be shielded from metabolic enzymes.

Link is any moiety which covalently binds together UC781 or an analog of UC781 and a phosphonate group. In the present invention, a link is intended to include atoms and molecules which can be used to covalently bind UC781 or an analog thereof at one end of the link to the $PO(R_1)(R_2)$ at the other end of the link. The link should not prevent the binding of the analog with its appropriate receptor. Examples of suitable links include, but are not limited to,

polymethylene [-(CH_2)$_n$, where n is 1-10], ester, amine, carbonate, carbamate, ether, olefin, aromatic ring, acetal, heteroatom containing ring or any combination of two or more of these units. Direct attachment of the PO(R_1)(R_2) is also possible. A skilled artisan will readily recognize other links which can be used in accordance with the present invention.

The following examples illustrate various aspects of the present invention and are not to be construed to limit the types of analogs that may employ this strategy of linking UC781 or an UC781 analog to a PO(R_1)(R_2) moiety in any manner whatsoever.

Preparation of compounds of type A may proceed via a link which can react with UC781 or an analog or intermediate thereof, to result in a covalent bond between the link and the drug-like compound. The link is also attached to the phosphorous containing moiety as shown in an example of type A, namely A1.

Preparation of N-3-((2-chlorophenoxy)methyl)-4-chlorophenyl-2-methyl-3-furancarbothioamide, compound 12 in UC781 Scheme 1 and intermediates 2, 4-11, as per US Patent No. 6143780.

Step 1: Preparation of 2-chloro-5-nitrobenzoyl alcohol 30 g of 2-chloro-5-nitrobenzaldehyde was dissolved in 500 mL of methanol and cooled to 0°C. A solution of 10 g of sodium borohydride in 100 mL of water was then added dropwise over 90 minutes while maintaining the temperature below 10°C. The resultant reaction mixture was then stirred for one hour, then acidified with 2N HCl and left stirring overnight. The solids were then, washed with water and dried, to produce 27 g of 2-chloro-5-nitrobenzyl alcohol as a white solid.

Step 2: Preparation of 2-chloro-5-nitrobenzoyl acetate 27 g of the 2-chloro-5-nitrobenzyl alcohol prepared above in Step 1, was dissolved in 122 mL of toluene. 22 mL of triethylamine was then added. The resultant reaction mixture was cooled to 20°C. and then a solution of 10.2 mL of acetyl chloride in 10 mL of toluene, was added dropwise, keeping the temperature below 20°C. The reaction mixture was then stirred overnight. 2.1 mL of triethylamine and 1.1 mL of acetyl chloride/toluene solution were then added and the reaction mixture was stirred for one hour. 100 mL of water was then added, followed by 50 mL of ether. The resulting organic phase was separated, washed with 2N HCl, aqueous sodium bicarbonate solution and water. The washed organic phase was then dried over magnesium sulfate and the solvent was evaporated, to produce 29.6 g of 2-chloro-5-nitrobenzoyl acetate as a white solid.

Step 3: Preparation of 5-amino-2-chlorobenzoyl acetate 24 g of iron powder was added to a solution of 1.6 mL of concentrated HCl, 16.8 mL of water, and 70 mL of ethanol. 29.6 g of the 2-chloro-5-nitrobenzoyl acetate prepared above in Step 2 dissolved in 45 mL of ethanol, was then added to the mixture in three equal portions. The resultant reaction mixture was refluxed for 5 hours. An additional 2.4 g of iron and 0.1 mL of concentrated HCl was then added to the reaction mixture. The reaction mixture was then refluxed for an additional one hour, filtered through Celite and evaporated. 100 mL of water was then added to the evaporated material and the resultant mixture was extracted with 100 mL of ether. The ether solution was washed with water, dried over magnesium sulfate, and evaporated, to produce 22.9 g of 5-amino-2-chlorobenzoyl acetate as an oil.

Step 4: Preparation of N-(3-acetoxymethyl-4-chlorophenyl)-2-methyl-3-furancarboxanilide. A solution of 22.8 g of the 5-amino-2-chlorobenzoyl acetate from Step 3 above and 17.2 mL of triethylamine in 118 mL ether was prepared and then added dropwise to a second solution of 16.6 g 2-methyl-3-thiophenecarboxylic acid chloride in 118 mL ether at 0°C. to 10°C.and the resultant mixture was stirred at room temperature overnight. 100 mL of water and 100 mL of ethyl acetate were then added to the mixture, the organic phase separated, washed with 2N hydrochloric acid and water, dried over magnesium sulfate, and the solvents removed *in vacuo*, to produce 29.87 g of N-(3-acetoxymethyl-4-chlorophenyl)-2-methyl-3-furancarboxamide as a beige solid.

Step 5: Preparation of N-(4-chloro-3-hydroxymethylphenyl)-2-methyl-3-furancarboxamide. A solution of 29 g of the N-(3-acetoxymethyl-4-chlorophenyl)-2-methyl-3-furancarboxamide prepared in Step 4 above and 14.5 g potassium hydroxide in 110 mL water, was prepared. The solution was then heated at 70°C. for 16 hours and then acidified with 2N hydrochloric. The resulting solid was collected, washed with water, and dried, producing 23.65 g of N-(4-chloro-3-hydroxymethylphenyl)-2-methyl-3-furancarboxamide as a white solid.

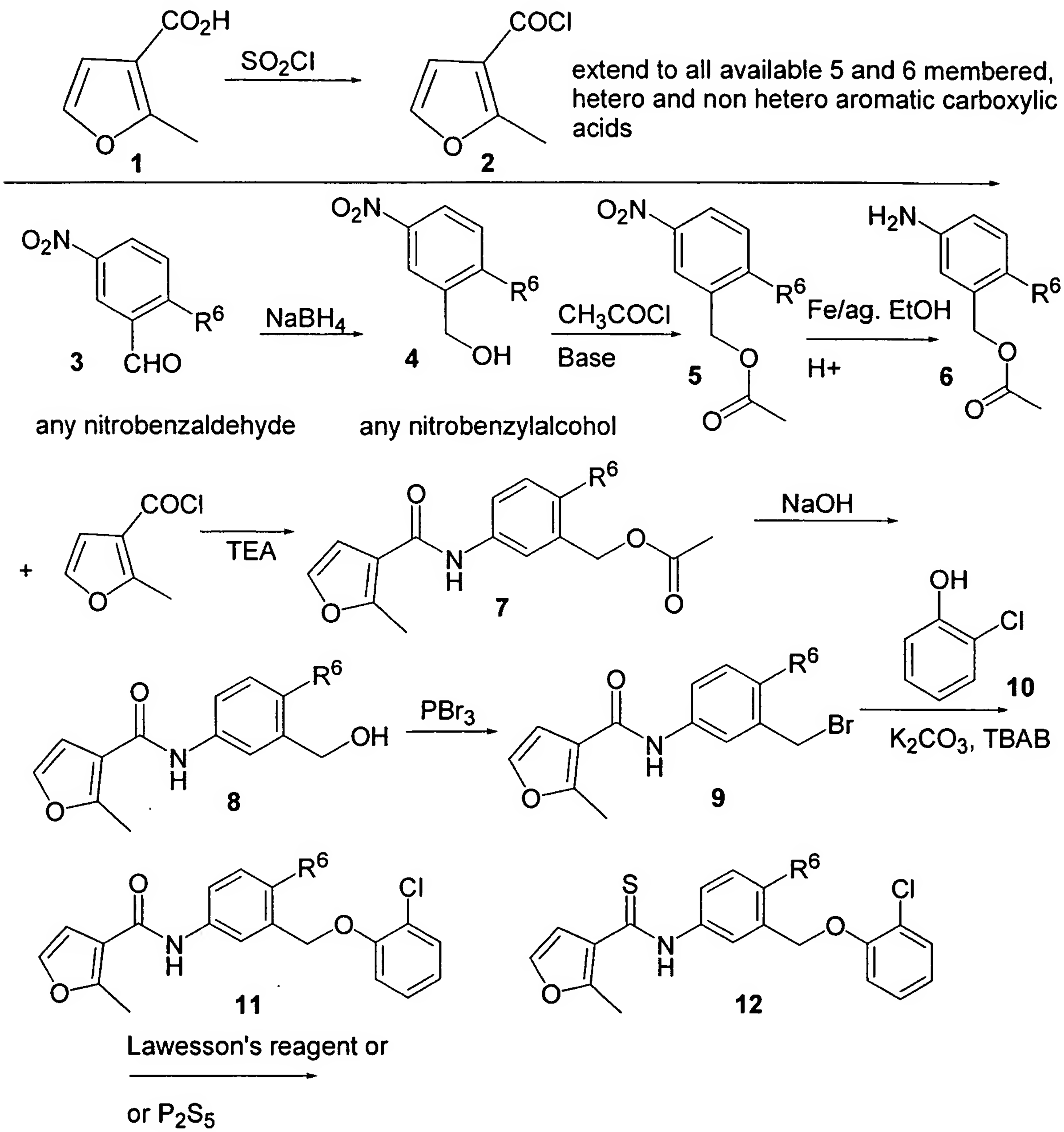
Step 6: Preparation of N-(3-bromomethyl-4-chlorophenyl)-2-methyl-3-furancarboxamide. 12 g of the N-(4-chloro-3-hydroxymethylphenyl)-2-methyl-3-furancarboxamide prepared in Step 5 above, was dissolved in 180 mL ethyl acetate. 1.8 mL of phosphorus tribromide was then added. The resultant mixture was stirred for 90 minutes at room temperature. 100 mL of water was then added to the mixture. The resultant organic phase was separated, washed with water, aqueous sodium bicarbonate solution and water, and then dried

over magnesium sulfate. The solvent was evaporated off to produce 12.97 g of N-(3-bromomethyl-4-chlorophenyl)-2-methyl-3-furancarboxamide as a solid.

Step 7: Preparation of N-3-((2-chlorophenoxy)methyl)-4-chlorophenyl-2-methyl-3-furancarboxamide. 2 g of the N-(3-bromomethyl-4-chlorophenyl)-2-methyl-3-furancarboxamide produced in Step 6, was dissolved in 20 mL of 2-butanone to produce a solution. 0.84 g of potassium carbonate, 0.79 g of 2-chlorophenol and 0.2 g of tetrabutylammonium bromide were then added to the solution. The resultant reaction mixture was stirred at room temperature overnight, the solvents removed *in vacuo*, and the residue extracted with ethyl acetate, to produce a second solution. This second solution was washed with 2N aqueous sodium hydroxide and water, and then dried over magnesium sulfate. The solvent was removed to produce 2.7 g of a solid, which was purified by dissolving in ethyl acetate:hexane (20:80) and running the resultant solution through a plug of silica gel. Removal of solvent produced 2.0 g of N-3-((2-chlorophenoxy)methyl)-4-chlorophenyl-2-methyl-3-furancarboxamid e as a white solid.

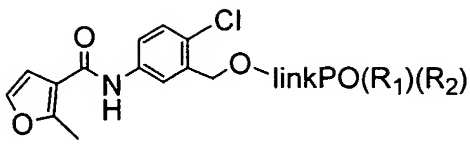
Step 8: Preparation of N-3-((2-chlorophenoxy)methyl)-4-chlorophenyl-2-methyl-3-furancarbothioamide. 1.5 g of the N-3-((2-chlorophenoxy)methyl)-4-chlorophenyl-2-methyl-3-furancarboxamide prepared in Step 7 above, 0.8 g of Lawesson's reagent (0.8 g) and 1.6 g of sodium bicarbonate were added to 35 mL of toluene, and the resultant reaction mixture was refluxed for five hours. The reaction mixture was then passed through a plug of neutral aluminum oxide, eluted with 1:1 ether/hexane and purified by column chromatography on silica gel, to produce 0.77 g of N-3-((2-chlorophenoxy)methyl)-4-chlorophenyl-2-methyl-3-furancarbothioamide.

UC781 Scheme 1

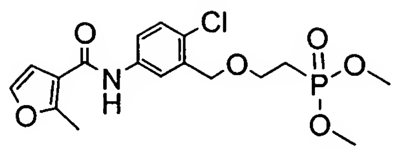


The above protocol can easily be modified to attach the link- $PO(R_1)(R_2)$.

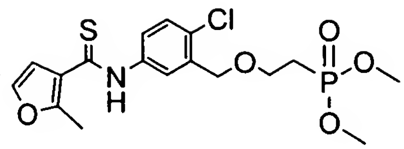
To prepare compounds of type A in UC781 Illustration 1, the following route is performed. Compound 8 above, when R^6 is chloro, is transformed into a triflate by reacting it with triflic anhydride and 2,6 lutidine in dichloromethane at -40°C. The addition of hydroxyethyldimethoxyphosphonate will effect the attachment of the link $PO(R_1)(R_2)$ group. Treatment with Lawesson's reagent as above will provide compound A2.



Type A



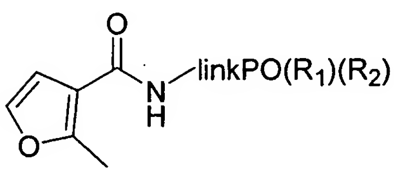
Example A1



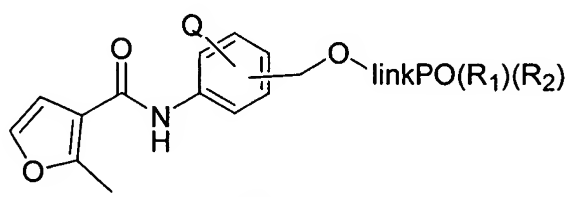
Example A2

UC781 Illustration 1

By replacing 2-chloro 5-nitrobenzaldehyde with other nitrobenzaldehyes and following a similar procedure as that used to make compound A2, the relative positions of attachment of the ether and the amide is changed. Furthermore, the chloro substituent shown as R^6 above is switched to other positions, and other substituents are used in combination with or without the chloro atom or other substituents anywhere on the ring (shown as Q below). This would allow for compounds of type B2 of UC781 Illustration 2 to be prepared. As with all analogs that are amenable to such treatment, Lawesson's reagent would then be used to convert to the corresponding sulfamide.



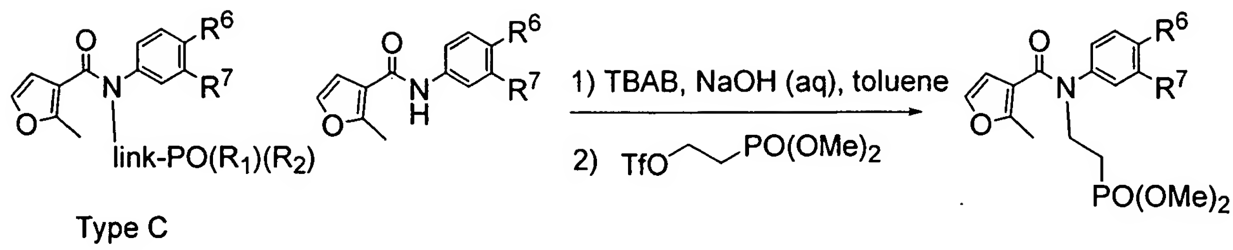
Type B1



Type B2

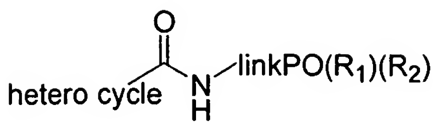
UC781 Illustration 2

Type B1 compounds would include Type B2 and are prepared using the above steps with the center aryl ring being considered part of the link. Prior to treatment with Lawesson's reagent the amide proton is abstracted by treatment with base to allow for attachment of the $PO(R_1)(R_2)$ moiety. Lawesson's reagent would then be used to convert to the corresponding sulfamide. This would allow for compounds of the general form Type C shown in UC781 Illustration 3.

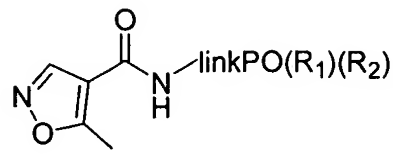


UC781 Illustration 3

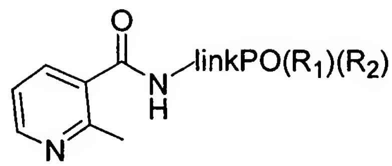
The furan ring of UC781 is switched to 5 or 6-membered heterocycles easily by substituting different heterocyclic acid chlorides for 2-methyl-3-thiophenecarboxylic acid chloride in step 4 in the above written synthesis of N-3-((2-chlorophenoxy)methyl)-4-chlorophenyl-2-methyl-3-furancarbothioamide. This will afford Type D compounds as exemplified below. The link $PO(R_1)(R_2)$ moiety is attached directly to the heterocycle by starting with for example the diester of the desired heterocycle. Mono acid formation of the heterocycle by hydrolysis of one ester would allow for attachment of the $PO(R_1)(R_2)$ group. This would be followed by hydrolysis of the remaining ester by base, acid chloride formation as above and amide formation by reaction with the desired amine. D1, a specific exemplification of Type D compounds having in this case R_1 and R_2 = OMe and link = CH_2CH_2 is prepared as shown below in UC781 Illustration 4.



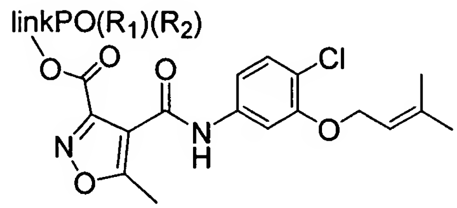
Type D



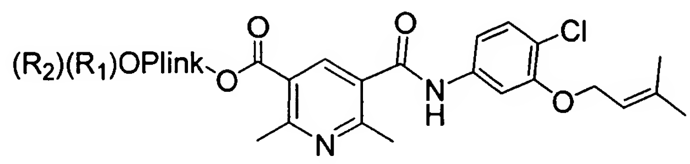
5-membered heterocycle



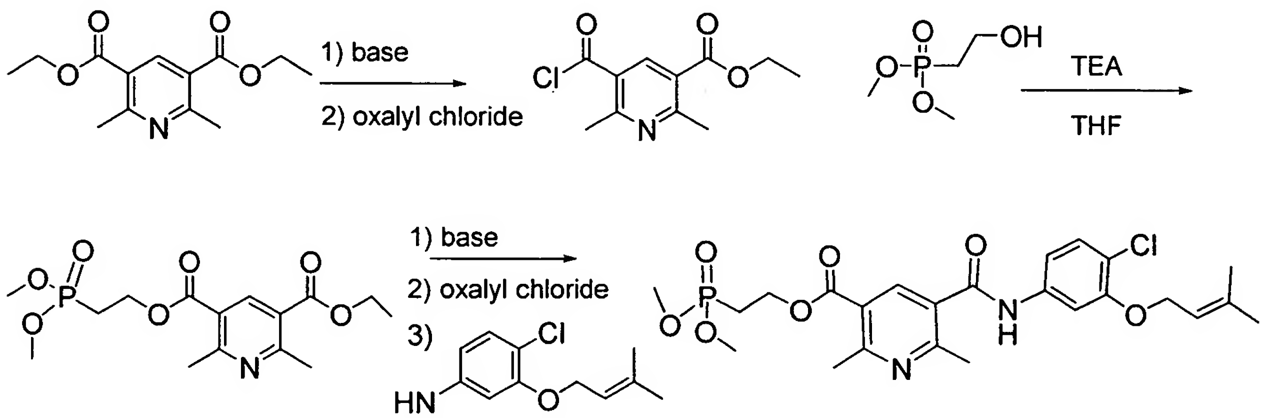
6-membered heterocycle



5-membered heterocycle
with linkPO(R_1)(R_2) attached at
heterocycle



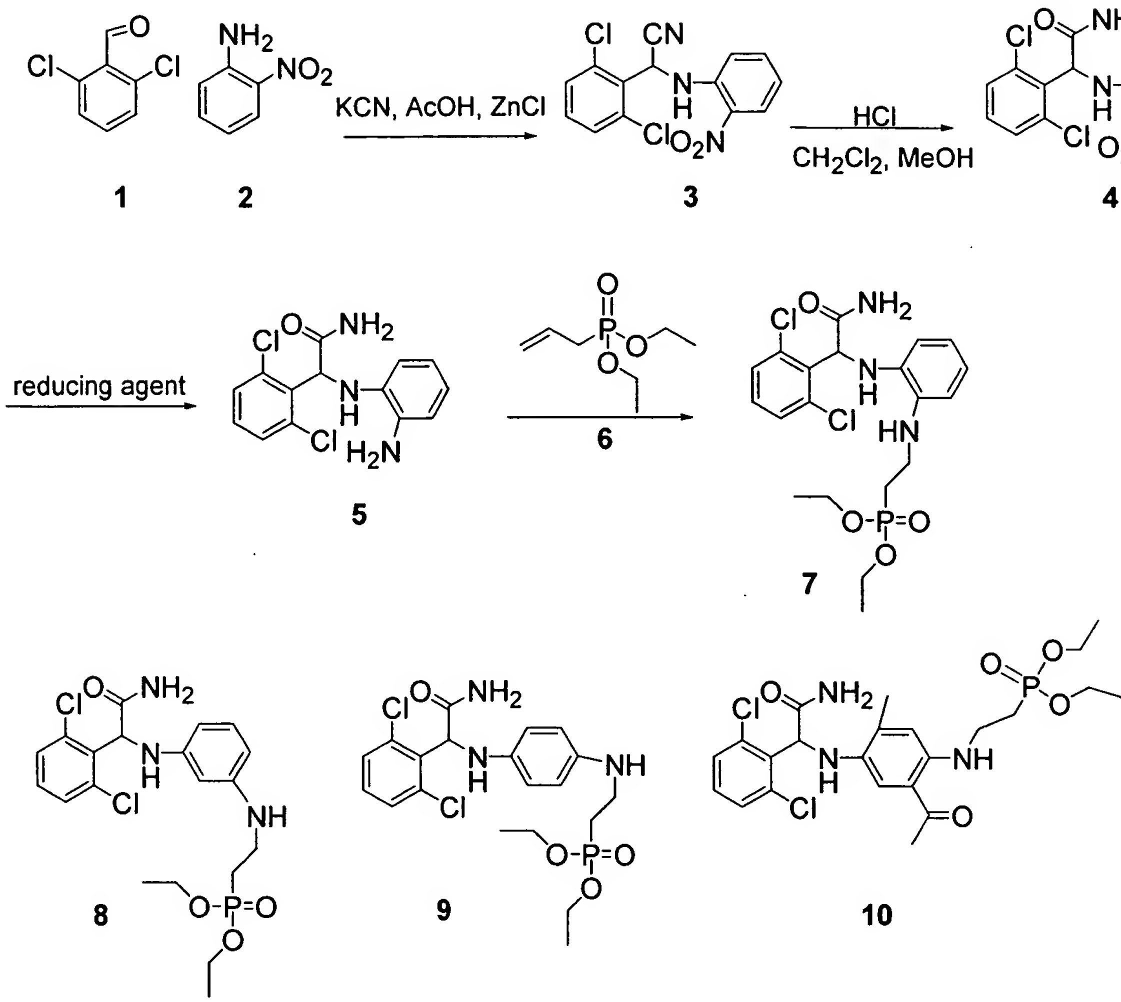
6-membered heterocycle
with linkPO(R_1)(R_2) attached at
heterocycle



UC781 Illustration 4

All amides shown can be converted to sulfamides by treatment with Lawesson's reagent.

UC781 Scheme 2



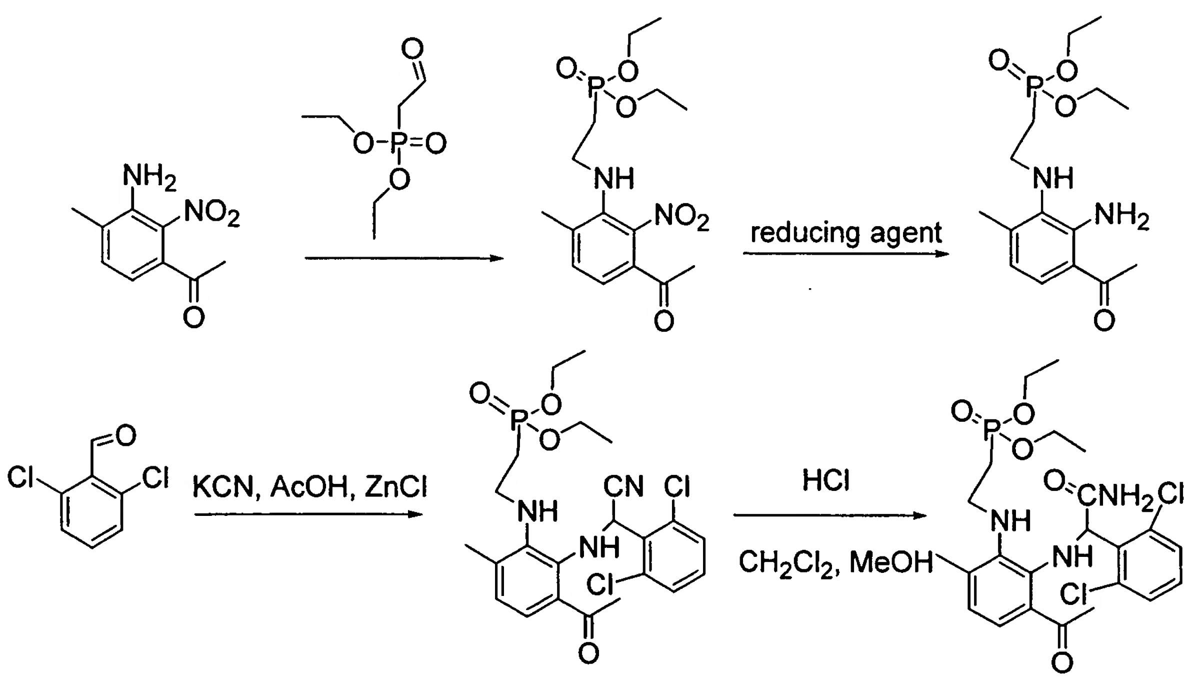
The details of the first two steps of UC781 Scheme 2 shown above are thoroughly covered in US Patent No. 5556886. The synthesis can be extended as shown to allow for the attachment of the link $PO(R_1)(R_2)$ at various sites on either aryl ring.

To attach on the ortho, meta or para positions of the ring that starts out as the substituted aniline, a moiety must be present that will allow for such an attachment of the $PO(R_1)(R_2)$ moiety. In this case a nitro group is used as an amine precursor. The reduction of the nitro can be effected by tin chloride and acetic acid in an appropriate solvent, or through some other catalytic hydrogenation method. From there, compounds such as compound 5 with a free anilino NH_2 can be reacted with, for example, a commercially available phosphonate such as compound 6 above in a reductive amination reaction. This reductive amination is performed using

dichloroethane as solvent, and after stirring under dry conditions, sodium cyanoborohydride and acetic acid is added to complete the reaction giving compound 7. Using commercially available meta and para nitroanilines leads to compounds 8, 9 and 10. Other substitution patterns are also possible. Also, other means of attachment are also possible to attach the drug-like compound to the $PO(R_1)(R_2)$ piece. By varying the position of the nitro group, the $PO(R_1)(R_2)$ is attached at any position on the anilino ring. UC781 Scheme 3 below contains examples of nitroanilines that allow for the attachment at various positions.

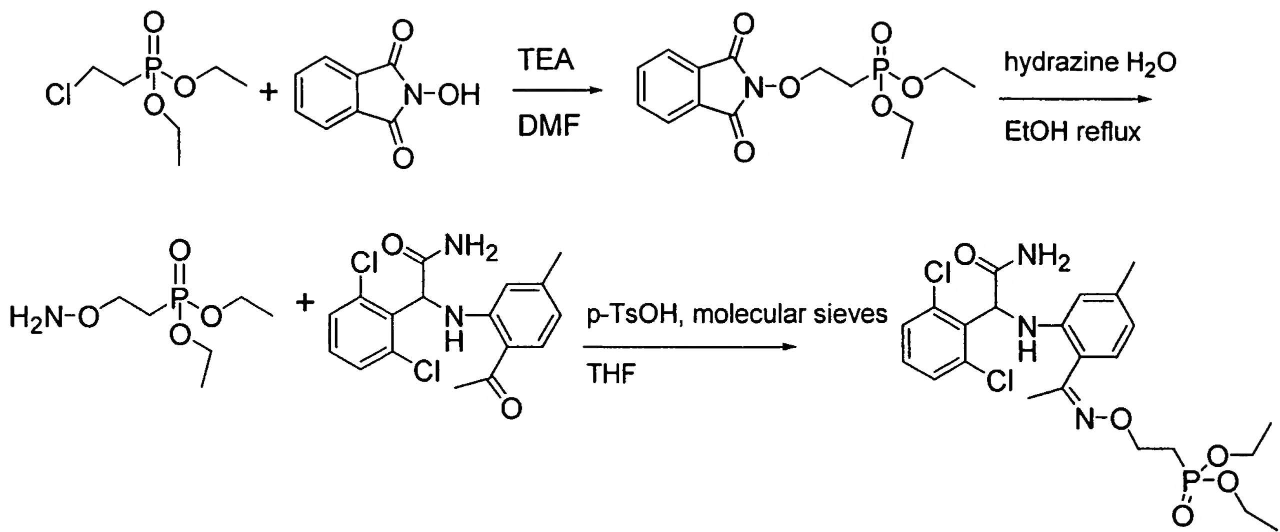
Alternatively, the nitroanilines is attached to the $PO(R_1)(R_2)$ moiety prior to coupling with the aldehyde. The nitro is then reduced to form the aniline needed for coupling with the aldehyde. Hydrolysis of the cyano group to the amide is conducted as above, as illustrated in UC791 Scheme 2.

UC781 Scheme 3

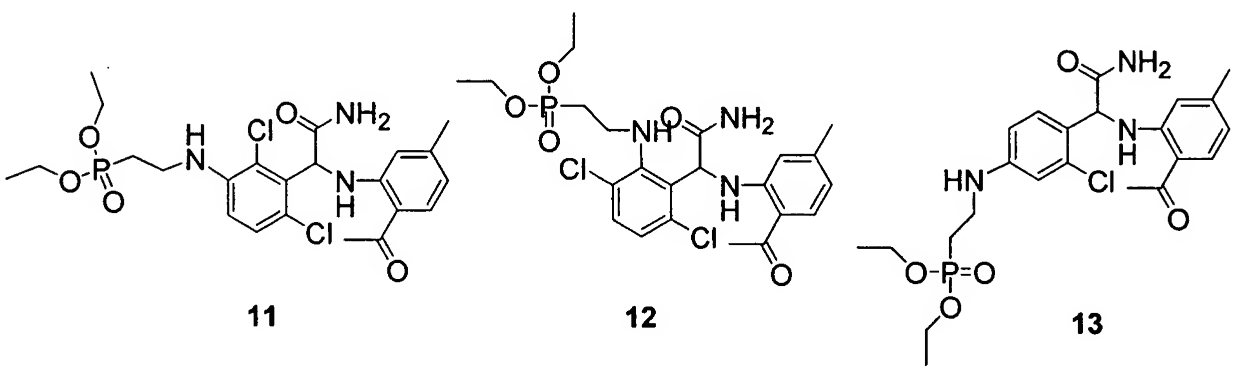


The ketone of Loviride or Loviride analogs also serves as a point of attachment for the $PO(R_1)(R_2)$ group. The synthesis of such an attachment is shown in UC781 Scheme 4.

UC781 Scheme 4



By using a variation of the benzaldehyde shown as compound 1 in UC781 Scheme 2, further points of attachment are also attainable. By using, for example, 2,6-dichloro (3,4, or 5 nitro) benzaldehyde, and following UC781 Scheme 2, the $PO(R_1)(R_2)$ is attached at any position of the ring which starts out as the benzaldehyde. Further examples of compounds that can be made in this way are compounds 11, 12 and 13, shown in UC781 Illustration 5 below.



11 **12** **13**

UC781 Illustration 5

Capravirine-like compounds

The drugs which can be derivatized in accord with the present invention must contain at least one functional group capable of linking, *i.e.* bonding to the phosphorus atom in the phosphonate group. The phosphonate derivatives of Formula I and II may cleave *in vivo* in

stages after they have reached the desired site of action, *i.e.* inside a cell. One mechanism of action inside a cell may entail a first cleavage, *e.g.*, by esterase, to provide a negatively-charged "locked-in" intermediate. Cleavage of a terminal ester grouping in Formula I or II thus affords an unstable intermediate which releases a negatively charged "locked in" intermediate.

After passage inside a cell, intracellular enzymatic cleavage or modification of the phosphonate prodrug compound may result in an intracellular accumulation of the cleaved or modified compound by a "trapping" mechanism. The cleaved or modified compound may then be "locked-in" the cell, *i.e.* accumulate in the cell by a significant change in charge, polarity, or other physical property change which decreases the rate at which the cleaved or modified compound can exit the cell, relative to the rate at which it entered as the phosphonate prodrug. Other mechanisms by which a therapeutic effect are achieved may be operative as well. Enzymes which are capable of an enzymatic activation mechanism with the phosphonate prodrug compounds of the invention include, but are not limited to, amidases, esterases, microbial enzymes, phospholipases, cholinesterases, and phosphatases.

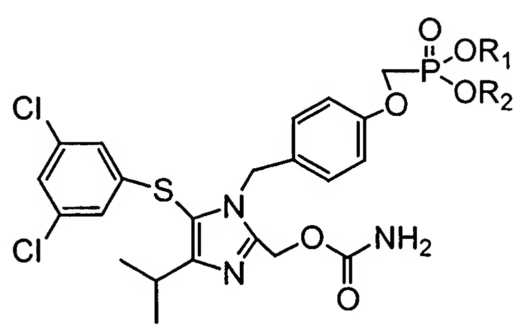
In selected instances in which the drug is of the nucleoside type, such as is the case of zidovudine and numerous other antiretroviral agents, it is known that the drug is activated *in vivo* by phosphorylation. Such activation may occur in the present system by enzymatic conversion of the "locked-in" intermediate with phosphokinase to the active phosphonate diphosphate and/or by phosphorylation of the drug itself after its release from the "locked-in" intermediate as described above. In either case, the original nucleoside-type drug will be converted, via the derivatives of this invention, to the active phosphorylated species.

From the foregoing, it will be apparent that many different drugs can be derivatized in accord with the present invention. Numerous such drugs are specifically mentioned herein. However, it should be understood that the discussion of drug families and their specific members for derivatization according to this invention is not intended to be exhaustive, but merely illustrative.

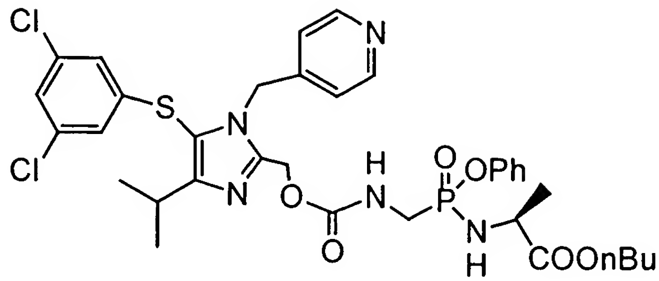
As another example, when the selected drug contains multiple reactive hydroxyl functions, a mixture of intermediates and final products may again be obtained. In the unusual case in which all hydroxy groups are approximately equally reactive, there is not expected to be a single, predominant product, as each mono-substituted product will be obtained in approximate by equal amounts, while a lesser amount of multiply-substituted product will also result.

Generally speaking, however, one of the hydroxyl groups will be more susceptible to substitution than the other(s), *e.g.*, a primary hydroxyl will be more reactive than a secondary hydroxyl, an unhindered hydroxyl will be more reactive than a hindered one. Consequently, the major product will be a mono-substituted one in which the most reactive hydroxyl has been derivatized while other mono-substituted and multiply-substituted products may be obtained as minor products.

The invention includes Capravirine-like compounds (CLC). Capravirine is described in US Patent No. 5910506, US Patent No. 6083958, US Patent No. 6147097, WO 96/10019, and US Patent No. 5472965, as well as patent applications and granted patents which are equivalents of, or related by priority claims thereto. The definition of CLC means not only the generic disclosures cited above but also each and every species set forth within the cases making up the enumerated groups. CLC compositions of the invention include a phosphonate group covalently attached as detailed in Formula I. The phosphonate group may be a phosphonate prodrug moiety. The prodrug moiety may be sensitive to hydrolysis, such as, but not limited to a pivaloyloxymethyl carbonate (POC) or POM group. Alternatively, the prodrug moiety may be sensitive to enzymatic potentiated cleavage, such as a lactate ester or a phosphonamidate-ester group. An exemplary group of phosphonate diester CLC compounds anticipated by the present invention includes:



An exemplary phosphonamidate-ester CLC compound anticipated by the present invention includes:



Scheme General Section

General aspects of these exemplary methods are described below and in the Examples. Each of the products of the following processes is optionally separated, isolated, and/or purified prior to its use in subsequent processes.

The terms “treated”, “treating”, “treatment”, and the like, mean contacting, mixing, reacting, allowing to react, bringing into contact, and other terms common in the art for indicating that one or more chemical entities is treated in such a manner as to convert it to one or more other chemical entities. This means that “treating compound one with compound two” is synonymous with “allowing compound one to react with compound two”, “contacting compound one with compound two”, “reacting compound one with compound two”, and other expressions common in the art of organic synthesis for reasonably indicating that compound one was “treated”, “reacted”, “allowed to react”, etc., with compound two.

“Treating” indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal concentrations (0.01M to 10M, typically 0.1M to 1M), temperatures (-100°C to 250°C, typically -78°C to 150°C, more typically -78°C to 100°C, still more typically 0°C to 100°C), reaction vessels (typically glass, plastic, metal), solvents, pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or argon for oxygen or water sensitive), etc., are intended unless otherwise indicated. The knowledge of similar reactions known in the art of organic synthesis is used in selecting the conditions and apparatus for “treating” in a given process. In particular, one of ordinary skill in the art of organic synthesis selects conditions and apparatus reasonably expected to successfully carry out the chemical reactions of the described processes based on the knowledge in the art.

Modifications of each of the exemplary schemes above and in the examples (hereafter “exemplary schemes”) leads to various analogs of the specific exemplary materials produce. The

above cited citations describing suitable methods of organic synthesis are applicable to such modifications.

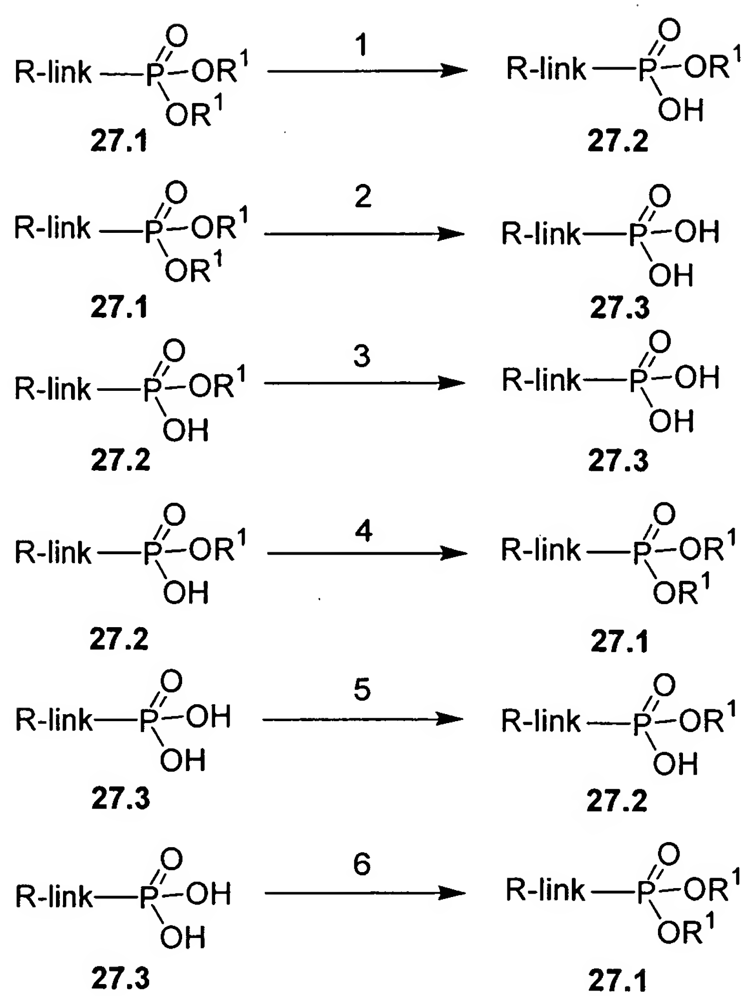
In each of the exemplary schemes it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example, size exclusion or ion exchange chromatography, high, medium, or low pressure liquid chromatography, small scale and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point, and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply techniques most likely to achieve the desired separation.

All literature and patent citations above are hereby expressly incorporated by reference at the locations of their citation. Specifically cited sections or pages of the above cited works are incorporated by reference with specificity. The invention has been described in detail sufficient to allow one of ordinary skill in the art to make and use the subject matter of the following Embodiments. It is apparent that certain modifications of the methods and compositions of the following Embodiments can be made within the scope and spirit of the invention.

Scheme Y1



Scheme Y1 shows the interconversions of certain phosphonate compounds: acids -$P(O)(OH)_2$; mono-esters -$P(O)(OR_1)(OH)$; and diesters -$P(O)(OR_1)_2$ in which the R^1 groups are independently selected, and defined herein before, and the phosphorus is attached through a carbon moiety (link, *i.e.* linker), which is attached to the rest of the molecule, *e.g.*, drug or drug intermediate (R). The R^1 groups attached to the phosphonate esters in Scheme Y1 may be changed using established chemical transformations. The interconversions may be carried out in the precursor compounds or the final products using the methods described below. The methods employed for a given phosphonate transformation depend on the nature of the substituent R^1. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester **27.1** into the corresponding phosphonate monoester **27.2** (Scheme Y1, Reaction 1) can be accomplished by a number of methods. For example, the ester **27.1** in which R^1 is an arylalkyl group such as benzyl, can be converted into the monoester compound **27.2** by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in *J. Org. Chem.*, 1995, 60:2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°C. The conversion of the diester **27.1** in which R^1 is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester **27.2** can be effected by treatment of the ester **27.1** with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters **27.2** in which one of the groups R^1 is arylalkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters **27.2** in which R^1 is alkyl, by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R^1 are alkenyl, such as allyl, can be converted into the monoester **27.2** in which R^1 is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in *J. Org. Chem.*, 38:3224 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester **27.1** or a phosphonate monoester **27.2** into the corresponding phosphonic acid **27.3** (Scheme Y1, Reactions 2 and 3) can be effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in *J. Chem. Soc., Chem. Comm.*, 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **27.2** in which R^1 is arylalkyl such as benzyl, can be converted into the corresponding phosphonic acid **27.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxane. A phosphonate monoester **27.2** in which R^1 is alkenyl such as, for example, allyl, can be converted into the phosphonic acid **27.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in *Helv. Chim. Acta.*, 68:618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **27.1** in which R^1 is benzyl is

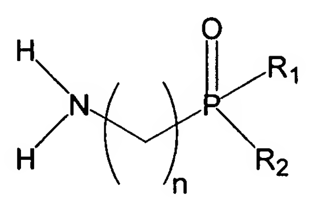
described in *J. Org. Chem.*, 24:434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **27.1** in which R^1 is phenyl is described in *J. Amer. Chem. Soc.*, 78:2336, 1956.

The conversion of a phosphonate monoester **27.2** into a phosphonate diester **27.1** (Scheme Y1, Reaction 4) in which the newly introduced R^1 group is alkyl, arylalkyl, or haloalkyl such as chloroethyl, can be effected by a number of reactions in which the substrate **27.2** is reacted with a hydroxy compound R^1OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **27.1** to the diester **27.1** can be effected by the use of the Mitsunobu reaction. The substrate is reacted with the hydroxy compound R^1OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **27.2** can be transformed into the phosphonate diester **27.1**, in which the introduced R^1 group is alkenyl or arylalkyl, by reaction of the monoester with the halide R^1Br, in which R^1 is as alkenyl or arylalkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **27.2** is transformed into the chloro analog $-P(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $-P(O)(OR^1)Cl$ is then reacted with the hydroxy compound R^1OH, in the presence of a base such as triethylamine, to afford the phosphonate diester **27.1**.

A phosphonic acid $-P(O)(OH)_2$ can be transformed into a phosphonate monoester $-P(O)(OR^1)(OH)$ (Scheme Y1, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester $-P(O)(OR^1)_2$ **27.1**, except that only one molar proportion of the component R^1OH or R^1Br is employed.

A phosphonic acid $-P(O)(OH)_2$ **27.3** can be transformed into a phosphonate diester $-P(O)(OR^1)_2$ **27.1** (Scheme Y1, Reaction 6) by a coupling reaction with the hydroxy compound R^1OH, in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids **27.3** can be transformed into phosphonic esters **27.1** in which R^1 is aryl, such as phenyl, by means of a coupling reaction employing, for example, phenol and dicyclohexylcarbodiimide in pyridine at about 70°C. Alternatively, phosphonic acids **27.3** can be transformed into phosphonic esters **27.1** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, in the presence of a base such as cesium carbonate, to afford the phosphonic ester **27.1**.

Amino alkyl phosphonate compounds 809:



809

are a generic representative of compounds 811, 813, 814, 816 and 818. Some methods to prepare embodiments of 809 are shown in Scheme Y2. Commercial amino phosphonic acid 810 was protected as carbamate 811. The phosphonic acid 811 was converted to phosphonate 812 upon treatment with ROH in the presence of DCC or other conventional coupling reagents. Coupling of phosphonic acid 811 with esters of amino acid 820 provided bisamidate 817. Conversion of acid 811 to bisphenyl phosphonate followed by hydrolysis gave mono-phosphonic acid 814 (Cbz = $C_6H_5CH_2C(O)$–), which was then transformed to mono-phosphonic amidate 815. Carbamates 813, 816 and 818 were converted to their corresponding amines upon hydrogenation. Compounds 811, 813, 814, 816 and 818 are useful intermediates to form the phosphonate compounds of the invention.

<u>Preparation of carboalkoxy-substituted phosphonate bisamidates, monoamidates, diesters and monoesters</u>

A number of methods are available for the conversion of phosphonic acids into amidates and esters. In one group of methods, the phosphonic acid is either converted into an isolated

activated intermediate such as a phosphoryl chloride, or the phosphonic acid is activated *in situ* for reaction with an amine or a hydroxy compound.

The conversion of phosphonic acids into phosphoryl chlorides is accomplished by reaction with thionyl chloride, for example as described in *J. Gen. Chem. USSR*, 1983, 53, 480, *Zh. Obschei Khim.*, 1958, 28, 1063, or *J. Org. Chem.*, 1994, 59, 6144, or by reaction with oxalyl chloride, as described in *J. Am. Chem. Soc.*, 1994, 116, 3251, or *J. Org. Chem.*, 1994, 59, 6144, or by reaction with phosphorus pentachloride, as described in *J. Org. Chem.*, 2001, 66, 329, or in *J. Med. Chem.*, 1995, 38, 1372. The resultant phosphoryl chlorides are then reacted with amines or hydroxy compounds in the presence of a base to afford the amidate or ester products.

Phosphonic acids are converted into activated imidazolyl derivatives by reaction with carbonyl diimidazole, as described in *J. Chem. Soc., Chem. Comm.*, 1991, 312, or *Nucleosides Nucleotides 2000*, 19, 1885. Activated sulfonyloxy derivatives are obtained by the reaction of phosphonic acids with trichloromethylsulfonyl chloride, as described in *J. Med. Chem.* 1995, 38, 4958, or with triisopropylbenzenesulfonyl chloride, as described in *Tetrahedron Lett.*, 1996, 7857, or *Bioorg. Med. Chem. Lett.*, 1998, 8, 663. The activated sulfonyloxy derivatives are then reacted with amines or hydroxy compounds to afford amidates or esters.

Alternatively, the phosphonic acid and the amine or hydroxy reactant are combined in the presence of a diimide coupling agent. The preparation of phosphonic amidates and esters by means of coupling reactions in the presence of dicyclohexyl carbodiimide is described, for example, in *J. Chem. Soc., Chem. Comm.*, 1991, 312, or *J. Med. Chem.*, 1980, 23, 1299 or *Coll. Czech. Chem. Comm.*, 1987, 52, 2792. The use of ethyl dimethylaminopropyl carbodiimide for activation and coupling of phosphonic acids is described in *Tetrahedron Lett.*, 2001, 42, 8841, or *Nucleosides Nucleotides*, 2000, 19, 1885.

A number of additional coupling reagents have been described for the preparation of amidates and esters from phosphonic acids. The agents include Aldrithiol-2, and PYBOP and BOP, as described in *J. Org. Chem.*, 1995, 60, 5214, and *J. Med. Chem.*, 1997, 40, 3842, mesitylene-2-sulfonyl-3-nitro-1,2,4-triazole (MSNT), as described in *J. Med. Chem.*, 1996, 39, 4958, diphenylphosphoryl azide, as described in *J. Org. Chem.*, 1984, 49, 1158, 1-(2,4,6-triisopropylbenzenesulfonyl-3-nitro-1,2,4-triazole (TPSNT) as described in *Bioorg. Med. Chem. Lett.*, 1998, 8, 1013, bromotris(dimethylamino)phosphonium hexafluorophosphate (BroP), as described in *Tetrahedron Lett.*, 1996, 37, 3997, 2-chloro-5,5-dimethyl-2-oxo-1,3,2-

dioxaphosphinane, as described in *Nucleosides Nucleotides* 1995, 14, 871, and diphenyl chlorophosphate, as described in *J. Med. Chem.*, 1988, 31, 1305.

Phosphonic acids are converted into amidates and esters by means of the Mitsonobu reaction, in which the phosphonic acid and the amine or hydroxy reactant are combined in the presence of a triaryl phosphine and a dialkyl azodicarboxylate. The procedure is described in *Org. Lett.*, 2001, 3, 643, or *J. Med. Chem.*, 1997, 40, 3842.

Phosphonic esters are also obtained by the reaction between phosphonic acids and halo compounds, in the presence of a suitable base. The method is described, for example, in *Anal. Chem.*, 1987, 59, 1056, or *J. Chem. Soc. Perkin Trans., I*, 1993, 19, 2303, or *J. Med. Chem.*, 1995, 38, 1372, or *Tetrahedron Lett.*, 2002, 43, 1161.

Schemes **1** - **4** illustrate the conversion of phosphonate esters and phosphonic acids into carboalkoxy-substituted phosphorobisamidates (Scheme **1**), phosphoroamidates (Scheme **2**), phosphonate monoesters (Scheme **3**) and phosphonate diesters, (Scheme **4**).

Scheme **1** illustrates various methods for the conversion of phosphonate diesters **1.1** into phosphorobisamidates **1.5**. The diester **1.1**, prepared as described previously, is hydrolyzed, either to the monoester **1.2** or to the phosphonic acid **1.6**. The methods employed for these transformations are described above. The monoester **1.2** is converted into the monoamidate **1.3** by reaction with an aminoester **1.9**, in which the group R^2 is H or alkyl, the group R^4 is an alkylene moiety such as, for example, $CHCH_3$, $CHPr^i$, $CH(CH_2Ph)$, $CH_2CH(CH_3)$ and the like, or a group present in natural or modified aminoacids, and the group R^5 is alkyl. The reactants are combined in the presence of a coupling agent such as a carbodiimide, for example dicyclohexyl carbodiimide, as described in *J. Am. Chem. Soc.*, 1957, 79, 3575, optionally in the presence of an activating agent such as hydroxybenztriazole, to yield the amidate product **1.3**. The amidate-forming reaction is also effected in the presence of coupling agents such as BOP, as described in *J. Org. Chem.*, 1995, 60, 5214, Aldrithiol, PYBOP and similar coupling agents used for the preparation of amides and esters. Alternatively, the reactants **1.2** and **1.9** are transformed into the monoamidate **1.3** by means of a Mitsonobu reaction. The preparation of amidates by means of the Mitsonobu reaction is described in *J. Med. Chem.*, 1995, 38, 2742. Equimolar amounts of the reactants are combined in an inert solvent such as tetrahydrofuran in the presence of a triaryl phosphine and a dialkyl azodicarboxylate. The thus-obtained monoamidate ester **1.3** is then transformed into amidate phosphonic acid **1.4**. The conditions used for the hydrolysis

reaction depend on the nature of the R^1 group, as described previously. The phosphonic acid amidate **1.4** is then reacted with an aminoester **1.9**, as described above, to yield the bisamidate product **1.5**, in which the amino substituents are the same or different.

An example of this procedure is shown in Scheme **1**, Example **1**. In this procedure, a dibenzyl phosphonate **1.14** is reacted with diazabicyclooctane (DABCO) in toluene at reflux, as described in *J. Org. Chem.*, 1995, 60, 2946, to afford the monobenzyl phosphonate **1.15**. The product is then reacted with equimolar amounts of ethyl alaninate **1.16** and dicyclohexyl carbodiimide in pyridine, to yield the amidate product **1.17**. The benzyl group is then removed, for example by hydrogenolysis over a palladium catalyst, to give the monoacid product **1.18**. This compound is then reacted in a Mitsonobu reaction with ethyl leucinate **1.19**, triphenyl phosphine and diethylazodicarboxylate, as described in *J. Med. Chem.*, 1995, 38, 2742, to produce the bisamidate product **1.20**.

Using the above procedures, but employing, in place of ethyl leucinate **1.19** or ethyl alaninate **1.16**, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

Alternatively, the phosphonic acid **1.6** is converted into the bisamidate **1.5** by use of the coupling reactions described above. The reaction is performed in one step, in which case the nitrogen-related substituents present in the product **1.5** are the same, or in two steps, in which case the nitrogen-related substituents can be different.

An example of the method is shown in Scheme **1**, Example **2**. In this procedure, a phosphonic acid **1.6** is reacted in pyridine solution with excess ethyl phenylalaninate **1.21** and dicyclohexylcarbodiimide, for example as described in *J. Chem. Soc., Chem. Comm.*, 1991, 1063, to give the bisamidate product **1.22**.

Using the above procedures, but employing, in place of ethyl phenylalaninate, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

As a further alternative, the phosphonic acid **1.6** is converted into the mono or bis-activated derivative **1.7**, in which Lv is a leaving group such as chloro, imidazolyl, triisopropylbenzenesulfonyloxy, etc. The conversion of phosphonic acids into chlorides **1.7** (Lv = Cl) is effected by reaction with thionyl chloride or oxalyl chloride and the like, as described in <u>Organic Phosphorus Compounds</u>, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17. The conversion of phosphonic acids into monoimidazolides **1.7** (Lv = imidazolyl) is described in *J. Med. Chem.*, 2002, 45, 1284 and in *J. Chem. Soc. Chem. Comm.*, 1991, 312. Alternatively, the

phosphonic acid is activated by reaction with triisopropylbenzenesulfonyl chloride, as described in *Nucleosides and Nucleotides*, 2000, 10, 1885. The activated product is then reacted with the aminoester **1.9**, in the presence of a base, to give the bisamidate **1.5**. The reaction is performed in one step, in which case the nitrogen substituents present in the product **1.5** are the same, or in two steps, via the intermediate **1.11**, in which case the nitrogen substituents can be different.

Examples of these methods are shown in Scheme **1**, Examples **3** and **5**. In the procedure illustrated in Scheme **1**, Example **3**, a phosphonic acid **1.6** is reacted with ten molar equivalents of thionyl chloride, as described in *Zh. Obschei Khim.*, 1958, 28, 1063, to give the dichloro compound **1.23**. The product is then reacted at reflux temperature in a polar aprotic solvent such as acetonitrile, and in the presence of a base such as triethylamine, with butyl serinate **1.24** to afford the bisamidate product **1.25**.

Using the above procedures, but employing, in place of butyl serinate **1.24**, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

In the procedure illustrated in Scheme **1**, Example **5**, the phosphonic acid **1.6** is reacted, as described in *J. Chem. Soc. Chem. Comm.*, 1991, 312, with carbonyl diimidazole to give the imidazolide **1.32**. The product is then reacted in acetonitrile solution at ambient temperature, with one molar equivalent of ethyl alaninate **1.33** to yield the monodisplacement product **1.34**. The latter compound is then reacted with carbonyl diimidazole to produce the activated intermediate **1.35**, and the product is then reacted, under the same conditions, with ethyl N-methylalaninate **1.33a** to give the bisamidate product **1.36**.

Using the above procedures, but employing, in place of ethyl alaninate **1.33** or ethyl N-methylalaninate **1.33a**, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

The intermediate monoamidate **1.3** is also prepared from the monoester **1.2** by first converting the monoester into the activated derivative **1.8** in which Lv is a leaving group such as halo, imidazolyl etc, using the procedures described above. The product **1.8** is then reacted with an aminoester **1.9** in the presence of a base such as pyridine, to give an intermediate monoamidate product **1.3**. The latter compound is then converted, by removal of the R^1 group and coupling of the product with the aminoester **1.9**, as described above, into the bisamidate **1.5**.

An example of this procedure, in which the phosphonic acid is activated by conversion to the chloro derivative **1.26**, is shown in Scheme 1, Example **4**. In this procedure, the phosphonic monobenzyl ester **1.15** is reacted, in dichloromethane, with thionyl chloride, as described in

Tetrahedron Lett., 1994, 35, 4097, to afford the phosphoryl chloride **1.26**. The product is then reacted in acetonitrile solution at ambient temperature with one molar equivalent of ethyl 3-amino-2-methylpropionate **1.27** to yield the monoamidate product **1.28**. The latter compound is hydrogenated in ethyl acetate over a 5% palladium on carbon catalyst to produce the monoacid product **1.29**. The product is subjected to a Mitsonobu coupling procedure, with equimolar amounts of butyl alaninate **1.30**, triphenyl phosphine, diethylazodicarboxylate and triethylamine in tetrahydrofuran, to give the bisamidate product **1.31**.

Using the above procedures, but employing, in place of ethyl 3-amino-2-methylpropionate **1.27** or butyl alaninate **1.30**, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

The activated phosphonic acid derivative **1.7** is also converted into the bisamidate **1.5** via the diamino compound **1.10**. The conversion of activated phosphonic acid derivatives such as phosphoryl chlorides into the corresponding amino analogs **1.10**, by reaction with ammonia, is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976. The diamino compound **1.10** is then reacted at elevated temperature with a haloester **1.12**, in a polar organic solvent such as dimethylformamide, in the presence of a base such as dimethylaminopyridine or potassium carbonate, to yield the bisamidate **1.5**.

An example of this procedure is shown in Scheme **1**, Example **6**. In this method, a dichlorophosphonate **1.23** is reacted with ammonia to afford the diamide **1.37**. The reaction is performed in aqueous, aqueous alcoholic or alcoholic solution, at reflux temperature. The resulting diamino compound is then reacted with two molar equivalents of ethyl 2-bromo-3-methylbutyrate **1.38**, in a polar organic solvent such as N-methylpyrrolidinone at ca. 150°C, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, to afford the bisamidate product **1.39**.

Using the above procedures, but employing, in place of ethyl 2-bromo-3-methylbutyrate **1.38**, different haloesters **1.12** the corresponding products **1.5** are obtained.

The procedures shown in Scheme **1** are also applicable to the preparation of bisamidates in which the aminoester moiety incorporates different functional groups. Scheme **1**, Example **7** illustrates the preparation of bisamidates derived from tyrosine. In this procedure, the monoimidazolide **1.32** is reacted with propyl tyrosinate **1.40**, as described in Example **5**, to yield the monoamidate **1.41**. The product is reacted with carbonyl diimidazole to give the imidazolide

1.42, and this material is reacted with a further molar equivalent of propyl tyrosinate to produce the bisamidate product **1.43**.

Using the above procedures, but employing, in place of propyl tyrosinate **1.40**, different aminoesters **1.9**, the corresponding products **1.5** are obtained. The aminoesters employed in the two stages of the above procedure can be the same or different, so that bisamidates with the same or different amino substituents are prepared.

Scheme **2** illustrates methods for the preparation of phosphonate monoamidates.

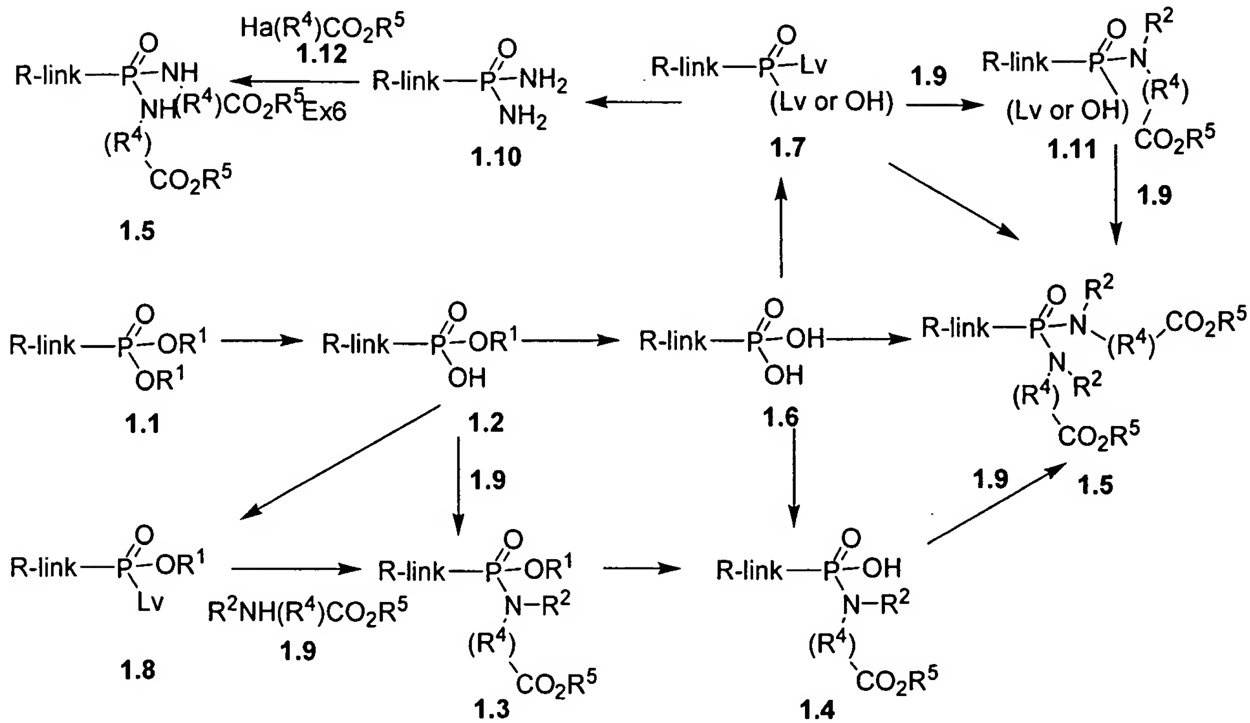
In one procedure, a phosphonate monoester **1.1** is converted, as described in Scheme **1**, into the activated derivative **1.8**. This compound is then reacted, as described above, with an aminoester **1.9**, in the presence of a base, to afford the monoamidate product **2.1**.

The procedure is illustrated in Scheme **2**, Example **1**. In this method, a monophenyl phosphonate **2.7** is reacted with, for example, thionyl chloride, as described in J. Gen. Chem. USSR., 1983, 32, 367, to give the chloro product **2.8**. The product is then reacted, as described in Scheme **1**, with ethyl alaninate **2.9**, to yield the amidate **2.10**.

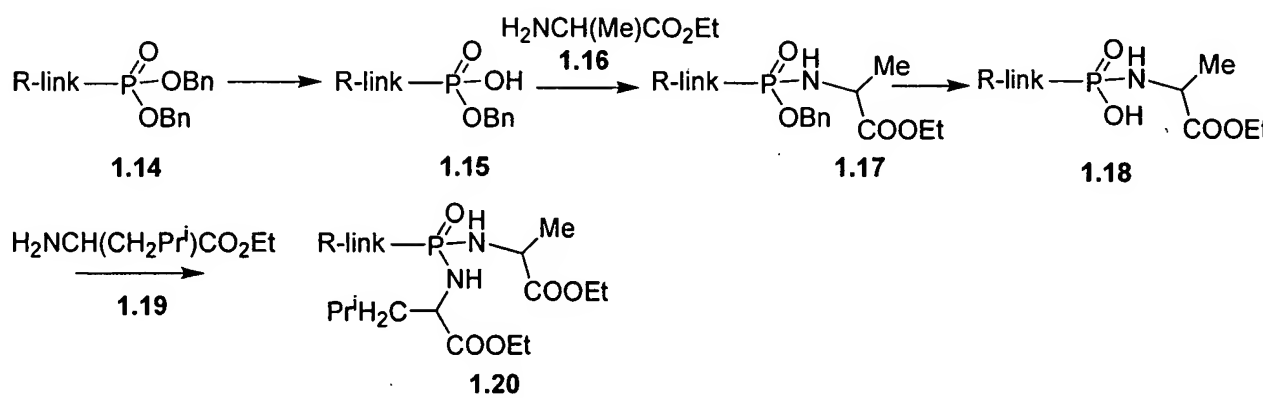
Using the above procedures, but employing, in place of ethyl alaninate **2.9**, different aminoesters **1.9**, the corresponding products **2.1** are obtained.

Alternatively, the phosphonate monoester **1.1** is coupled, as described in Scheme **1**, with an aminoester **1.9** to produce the amidate **2.1**. If necessary, the R^1 substituent is then altered, by initial cleavage to afford the phosphonic acid **2.2**. The procedures for this transformation depend on the nature of the R^1 group, and are described above. The phosphonic acid is then transformed into the ester amidate product **2.3**, by reaction with the hydroxy compound R^3OH, in which the group R^3 is aryl, heteroaryl, alkyl, cycloalkyl, haloalkyl etc, using the same coupling procedures (carbodiimide, Aldrithiol-2, PYBOP, Mitsonobu reaction etc) described in Scheme **1** for the coupling of amines and phosphonic acids.

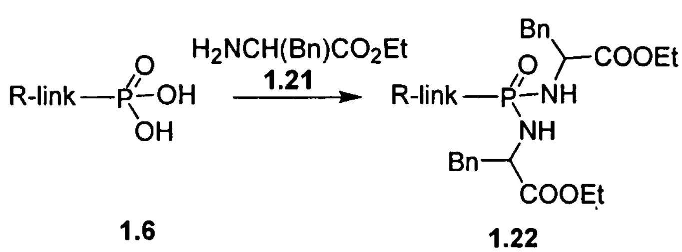
Scheme 1



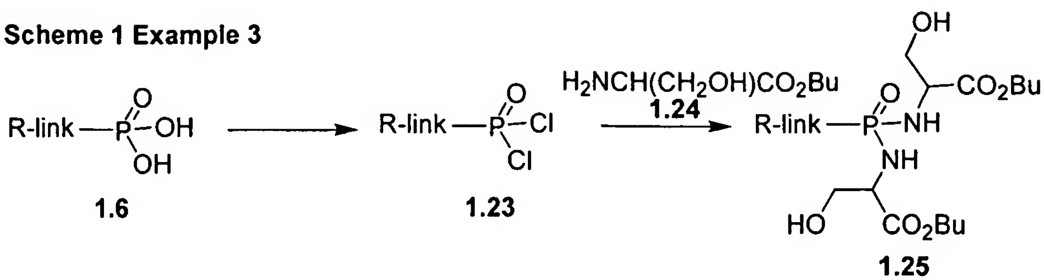
Scheme 1 Example 1



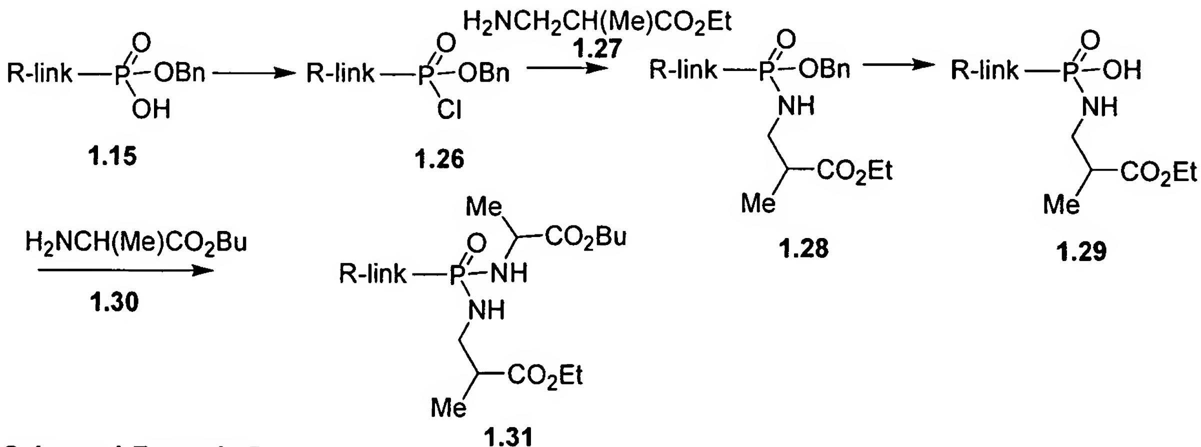
Scheme 1 Example 2



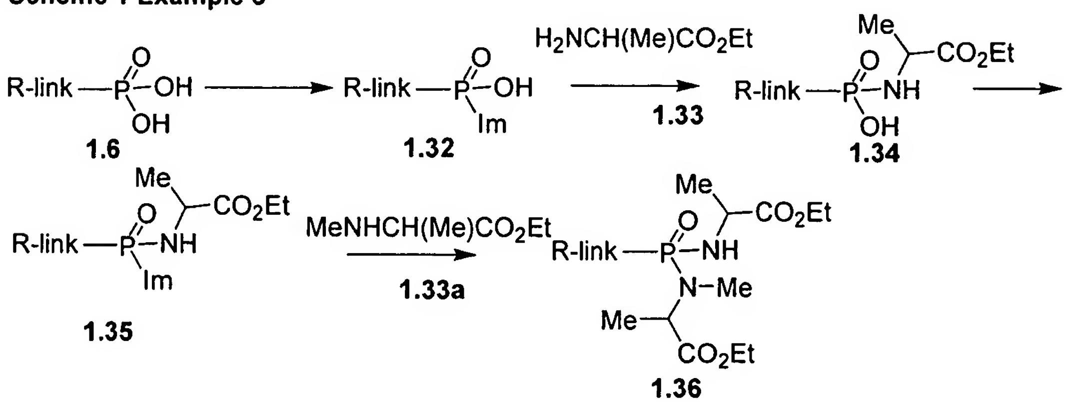
Scheme 1 Example 3



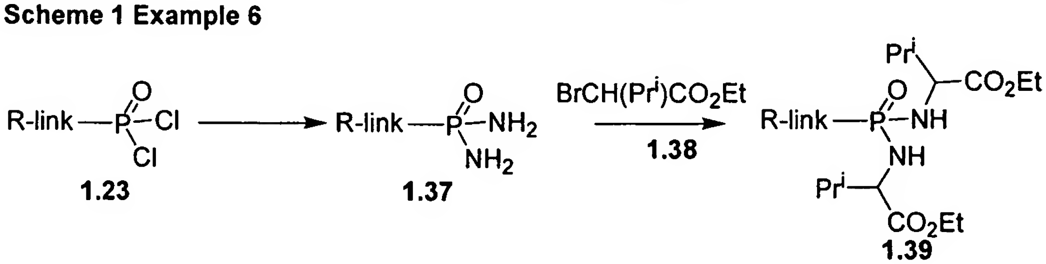
Scheme 1 Example 4



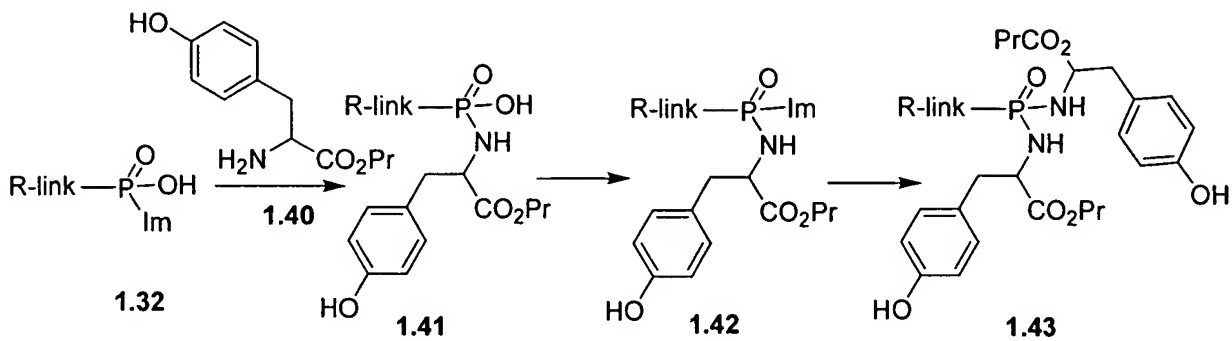
Scheme 1 Example 5



Scheme 1 Example 6



Scheme 1 Example 7



Examples of this method are shown in Scheme **2**, Examples and **2** and **3**. In the sequence shown in Example **2**, a monobenzyl phosphonate **2.11** is transformed by reaction with ethyl alaninate, using one of the methods described above, into the monoamidate **2.12**. The benzyl group is then removed by catalytic hydrogenation in ethyl acetate solution over a 5% palladium on carbon catalyst, to afford the phosphonic acid amidate **2.13**. The product is then reacted in dichloromethane solution at ambient temperature with equimolar amounts of 1-(dimethylaminopropyl)-3-ethylcarbodiimide and trifluoroethanol **2.14**, for example as described in *Tetrahedron Lett.*, 2001, 42, 8841, to yield the amidate ester **2.15**.

In the sequence shown in Scheme **2**, Example **3**, the monoamidate **2.13** is coupled, in tetrahydrofuran solution at ambient temperature, with equimolar amounts of dicyclohexyl carbodiimide and 4-hydroxy-N-methylpiperidine **2.16**, to produce the amidate ester product **2.17**.

Using the above procedures, but employing, in place of the ethyl alaninate product **2.12** different monoacids **2.2**, and in place of trifluoroethanol **2.14** or 4-hydroxy-N-methylpiperidine **2.16**, different hydroxy compounds R^3OH, the corresponding products **2.3** are obtained.

Alternatively, the activated phosphonate ester **1.8** is reacted with ammonia to yield the amidate **2.4**. The product is then reacted, as described in Scheme **1**, with a haloester **2.5**, in the presence of a base, to produce the amidate product **2.6**. If appropriate, the nature of the R^1 group is changed, using the procedures described above, to give the product **2.3**. The method is illustrated in Scheme **2**, Example **4**. In this sequence, the monophenyl phosphoryl chloride **2.18** is reacted, as described in Scheme **1**, with ammonia, to yield the amino product **2.19**. This material is then reacted in N-methylpyrrolidinone solution at 170°C with butyl 2-bromo-3-phenylpropionate **2.20** and potassium carbonate, to afford the amidate product **2.21**.

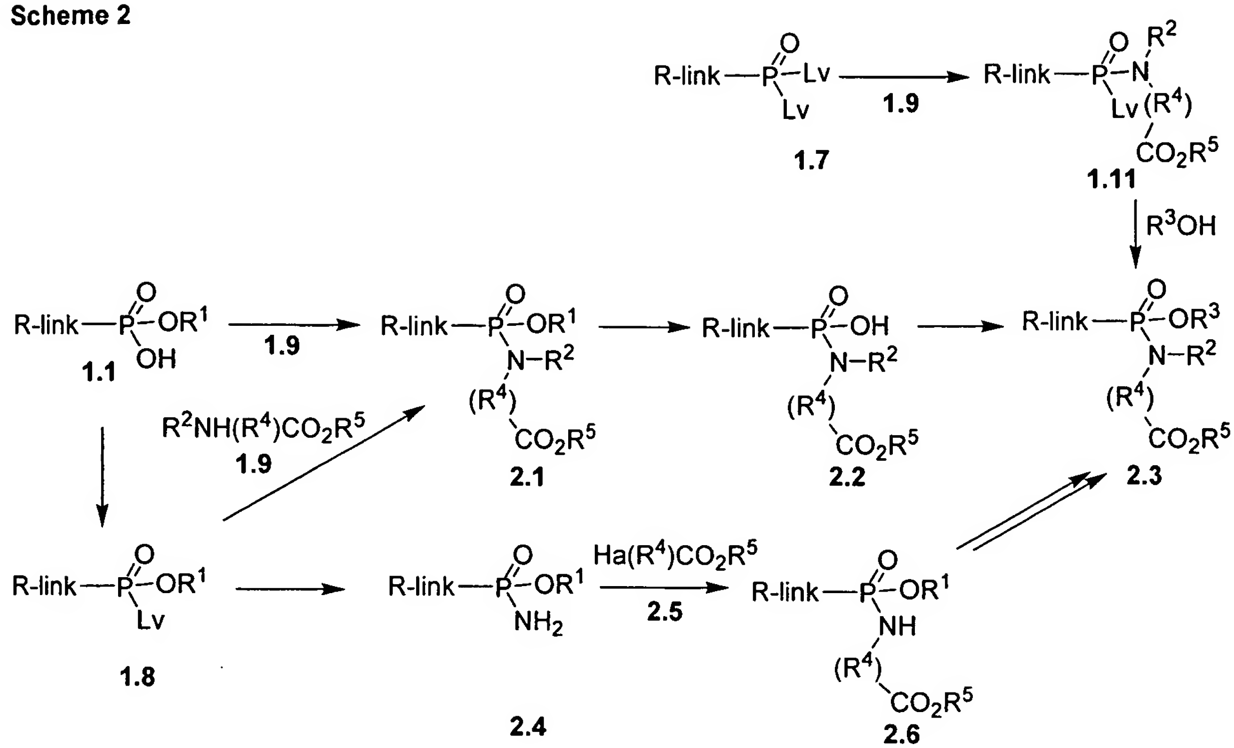
Using these procedures, but employing, in place of butyl 2-bromo-3-phenylpropionate **2.20**, different haloesters **2.5**, the corresponding products **2.6** are obtained.

The monoamidate products **2.3** are also prepared from the doubly activated phosphonate derivatives **1.7**. In this procedure, examples of which are described in Synlett., 1998, 1, 73, the intermediate **1.7** is reacted with a limited amount of the aminoester **1.9** to give the mono-displacement product **1.11**. The latter compound is then reacted with the hydroxy compound R^3OH in a polar organic solvent such as dimethylformamide, in the presence of a base such as diisopropylethylamine, to yield the monoamidate ester **2.3**.

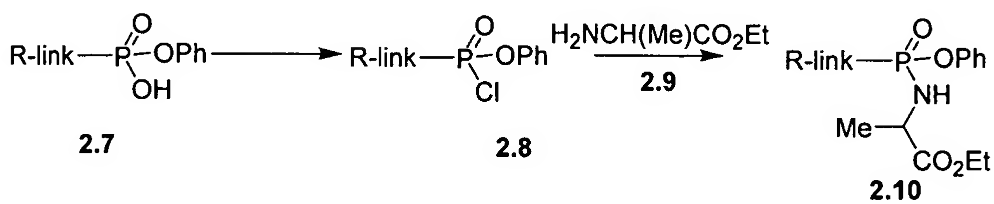
The method is illustrated in Scheme **2**, Example **5**. In this method, the phosphoryl dichloride **2.22** is reacted in dichloromethane solution with one molar equivalent of ethyl N-methyl tyrosinate **2.23** and dimethylaminopyridine, to generate the monoamidate **2.24**. The product is then reacted with phenol **2.25** in dimethylformamide containing potassium carbonate, to yield the ester amidate product **2.26**.

Using these procedures, but employing, in place of ethyl N-methyl tyrosinate **2.23** or phenol **2.25**, the aminoesters **1.9** and/or the hydroxy compounds R^3OH, the corresponding products **2.3** are obtained.

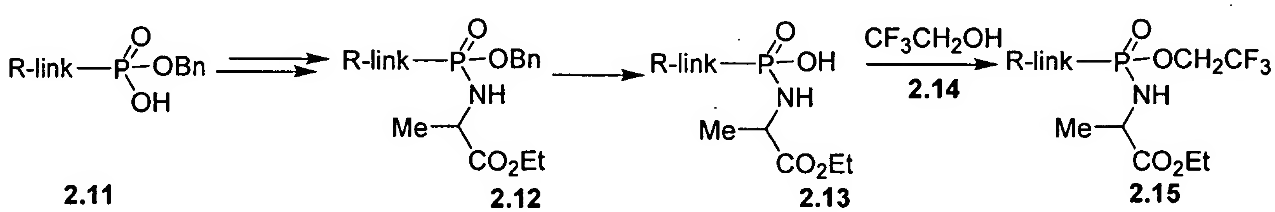
Scheme 2



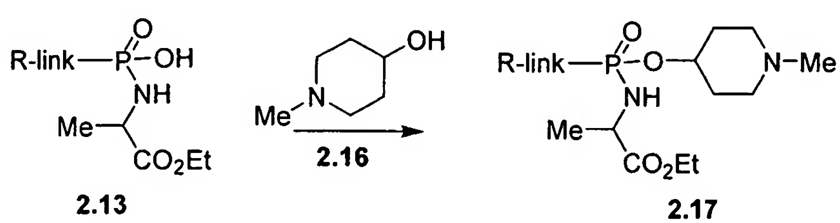
Scheme 2 Example 1



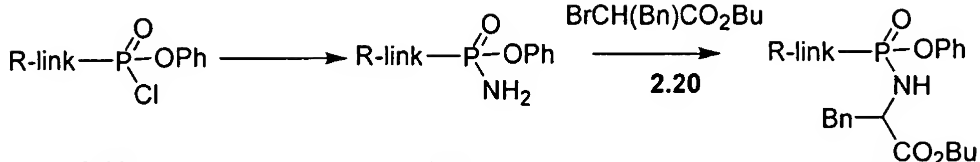
Scheme 2 Example 2



Scheme 2 Example 3

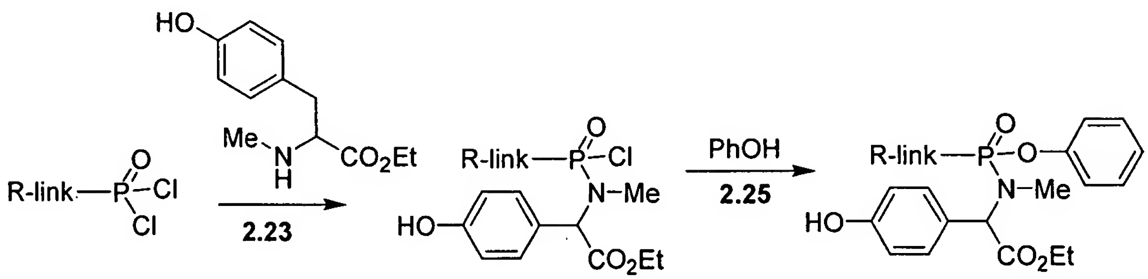


Scheme 2 Example 4



2.18 2.19 2.21

Scheme 2 Example 5



2.22 2.24 2.26

Scheme **3** illustrates methods for the preparation of carboalkoxy-substituted phosphonate diesters in which one of the ester groups incorporates a carboalkoxy substituent.

In one procedure, a phosphonate monoester **1.1**, prepared as described above, is coupled, using one of the methods described above, with a hydroxyester **3.1**, in which the groups R^4 and R^5 are as described in Scheme **1**. For example, equimolar amounts of the reactants are coupled in the presence of a carbodiimide such as dicyclohexyl carbodiimide, as described in *Aust. J. Chem.*, 1963, 609, optionally in the presence of dimethylaminopyridine, as described in *Tetrahedron Lett.*, 1999, 55, 12997. The reaction is conducted in an inert solvent at ambient temperature.

The procedure is illustrated in Scheme **3**, Example **1**. In this method, a monophenyl phosphonate **3.9** is coupled, in dichloromethane solution in the presence of dicyclohexyl carbodiimide, with ethyl 3-hydroxy-2-methylpropionate **3.10** to yield the phosphonate mixed diester **3.11**.

Using this procedure, but employing, in place of ethyl 3-hydroxy-2-methylpropionate **3.10**, different hydroxyesters **3.1**, the corresponding products **3.2** are obtained.

The conversion of a phosphonate monoester **1.1** into a mixed diester **3.2** is also accomplished by means of a Mitsonobu coupling reaction with the hydroxyester **3.1**, as described in *Org. Lett.*, 2001, 643. In this method, the reactants **1.1** and **3.1** are combined in a polar solvent such as tetrahydrofuran, in the presence of a triarylphosphine and a dialkyl azodicarboxylate, to give the mixed diester **3.2**. The R^1 substituent is varied by cleavage, using the methods described previously, to afford the monoacid product **3.3**. The product is then coupled, for example using methods described above, with the hydroxy compound R^3OH, to give the diester product **3.4**.

The procedure is illustrated in Scheme **3**, Example **2**. In this method, a monoallyl phosphonate **3.12** is coupled in tetrahydrofuran solution, in the presence of triphenylphosphine and diethylazodicarboxylate, with ethyl lactate **3.13** to give the mixed diester **3.14**. The product is reacted with tris(triphenylphosphine) rhodium chloride (Wilkinson catalyst) in acetonitrile, as described previously, to remove the allyl group and produce the monoacid product **3.15**. The latter compound is then coupled, in pyridine solution at ambient temperature, in the presence of dicyclohexyl carbodiimide, with one molar equivalent of 3-hydroxypyridine **3.16** to yield the mixed diester **3.17**.

Using the above procedures, but employing, in place of the ethyl lactate **3.13** or 3-hydroxypyridine, a different hydroxyester **3.1** and/or a different hydroxy compound R^3OH, the corresponding products **3.4** are obtained.

The mixed diesters **3.2** are also obtained from the monoesters **1.1** via the intermediacy of the activated monoesters **3.5**. In this procedure, the monoester **1.1** is converted into the activated compound **3.5** by reaction with, for example, phosphorus pentachloride, as described in *J. Org. Chem.*, 2001, 66, 329, or with thionyl chloride or oxalyl chloride (Lv = Cl), or with triisopropylbenzenesulfonyl chloride in pyridine, as described in *Nucleosides and Nucleotides*, 2000, 19, 1885, or with carbonyl diimidazole, as described in *J. Med. Chem.*, 2002, 45, 1284. The resultant activated monoester is then reacted with the hydroxyester **3.1**, as described above, to yield the mixed diester **3.2**.

The procedure is illustrated in Scheme **3**, Example **3**. In this sequence, a monophenyl phosphonate **3.9** is reacted, in acetonitrile solution at 70°C, with ten equivalents of thionyl chloride, so as to produce the phosphoryl chloride **3.19**. The product is then reacted with ethyl 4-

carbamoyl-2-hydroxybutyrate **3.20** in dichloromethane containing triethylamine, to give the mixed diester **3.21**.

Using the above procedures, but employing, in place of ethyl 4-carbamoyl-2-hydroxybutyrate **3.20**, different hydroxyesters **3.1**, the corresponding products **3.2** are obtained.

The mixed phosphonate diesters are also obtained by an alternative route for incorporation of the R^3O group into intermediates **3.3** in which the hydroxyester moiety is already incorporated. In this procedure, the monoacid intermediate **3.3** is converted into the activated derivative **3.6** in which Lv is a leaving group such as chloro, imidazole, and the like, as previously described. The activated intermediate is then reacted with the hydroxy compound R^3OH, in the presence of a base, to yield the mixed diester product **3.4**.

The method is illustrated in Scheme **3**, Example **4**. In this sequence, the phosphonate monoacid **3.22** is reacted with trichloromethanesulfonyl chloride in tetrahydrofuran containing collidine, as described in *J. Med. Chem.*, 1995, 38, 4648, to produce the trichloromethanesulfonyloxy product **3.23**. This compound is reacted with 3-(morpholinomethyl)phenol **3.24** in dichloromethane containing triethylamine, to yield the mixed diester product **3.25**.

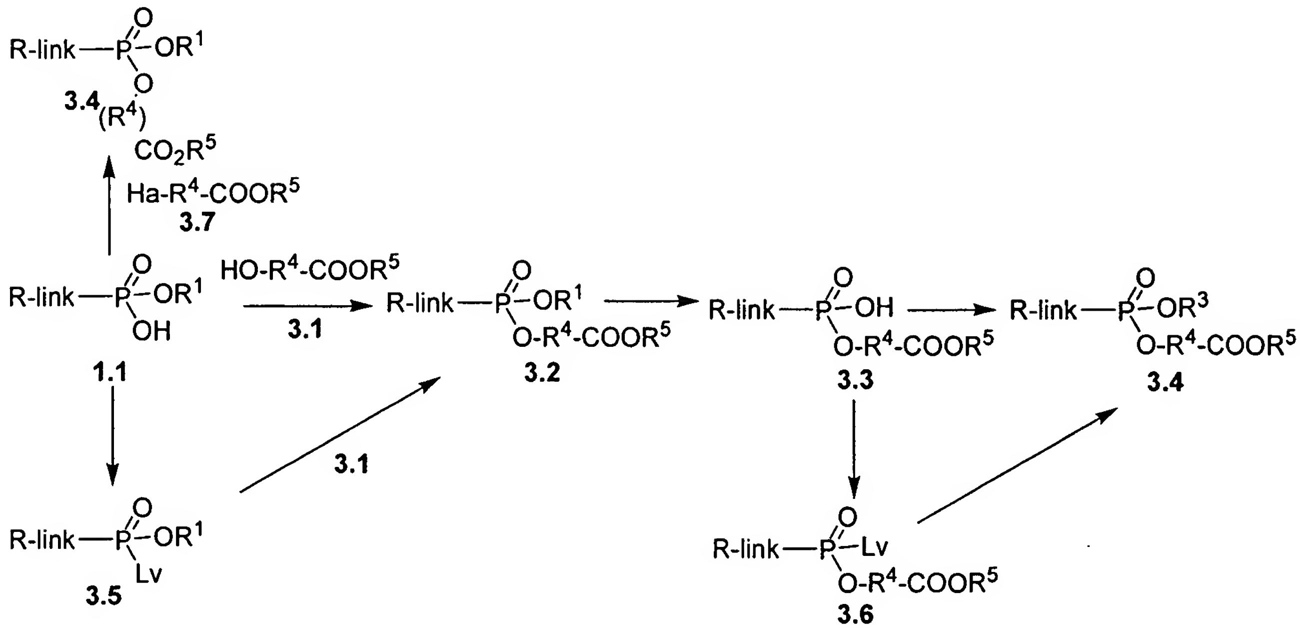
Using the above procedures, but employing, in place of with 3-(morpholinomethyl)phenol **3.24**, different carbinols R^3OH, the corresponding products **3.4** are obtained.

The phosphonate esters **3.4** are also obtained by means of alkylation reactions performed on the monoesters **1.1**. The reaction between the monoacid **1.1** and the haloester **3.7** is performed in a polar solvent in the presence of a base such as diisopropylethylamine, as described in *Anal. Chem.*, 1987, 59, 1056, or triethylamine, as described in *J. Med. Chem.*, 1995, 38, 1372, or in a non-polar solvent such as benzene, in the presence of 18-crown-6, as described in *Syn. Comm.*, 1995, 25, 3565.

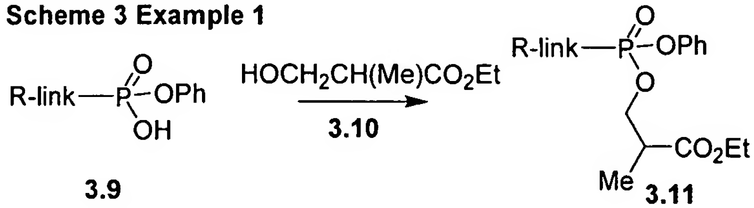
The method is illustrated in Scheme **3**, Example **5**. In this procedure, the monoacid **3.26** is reacted with ethyl 2-bromo-3-phenylpropionate **3.27** and diisopropylethylamine in dimethylformamide at 80°C to afford the mixed diester product **3.28**.

Using the above procedure, but employing, in place of ethyl 2-bromo-3-phenylpropionate **3.27**, different haloesters **3.7**, the corresponding products **3.4** are obtained.

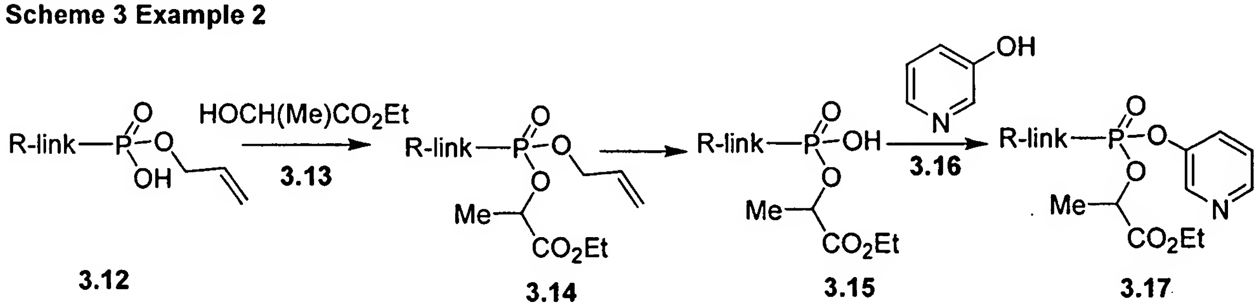
Scheme 3



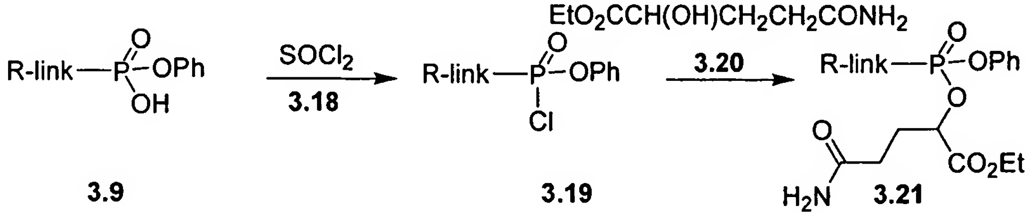
Scheme 3 Example 1



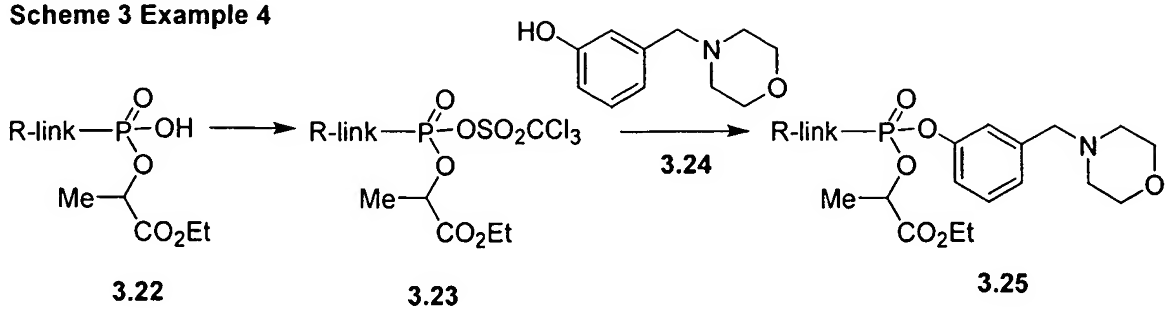
Scheme 3 Example 2



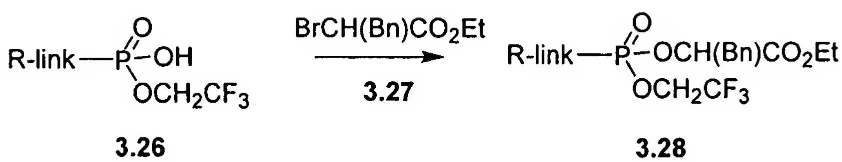
Scheme 3 Example 3



Scheme 3 Example 4



Scheme 3 Example 5



Scheme **4** illustrates methods for the preparation of phosphonate diesters in which both the ester substituents incorporate carboalkoxy groups.

The compounds are prepared directly or indirectly from the phosphonic acids **1.6**. In one alternative, the phosphonic acid is coupled with the hydroxyester **4.2**, using the conditions described previously in Schemes **1** - **3**, such as coupling reactions using dicyclohexyl carbodiimide or similar reagents, or under the conditions of the Mitsonobu reaction, to afford the diester product **4.3** in which the ester substituents are identical.

This method is illustrated in Scheme **4**, Example **1**. In this procedure, the phosphonic acid **1.6** is reacted with three molar equivalents of butyl lactate **4.5** in the presence of Aldrithiol-2 and triphenyl phosphine in pyridine at ca. 70°C, to afford the diester **4.6**.

Using the above procedure, but employing, in place of butyl lactate **4.5**, different hydroxyesters **4.2**, the corresponding products **4.3** are obtained.

Alternatively, the diesters **4.3** are obtained by alkylation of the phosphonic acid **1.6** with a haloester **4.1**. The alkylation reaction is performed as described in Scheme **3** for the preparation of the esters **3.4**.

This method is illustrated in Scheme **4**, Example **2**. In this procedure, the phosphonic acid **1.6** is reacted with excess ethyl 3-bromo-2-methylpropionate **4.7** and diisopropylethylamine

in dimethylformamide at ca. 80°C, as described in *Anal. Chem.*, 1987, 59, 1056, to produce the diester **4.8**.

Using the above procedure, but employing, in place of ethyl 3-bromo-2-methylpropionate **4.7**, different haloesters **4.1**, the corresponding products **4.3** are obtained.

The diesters **4.3** are also obtained by displacement reactions of activated derivatives **1.7** of the phosphonic acid with the hydroxyesters **4.2**. The displacement reaction is performed in a polar solvent in the presence of a suitable base, as described in Scheme **3**. The displacement reaction is performed in the presence of an excess of the hydroxyester, to afford the diester product **4.3** in which the ester substituents are identical, or sequentially with limited amounts of different hydroxyesters, to prepare diesters **4.3** in which the ester substituents are different.

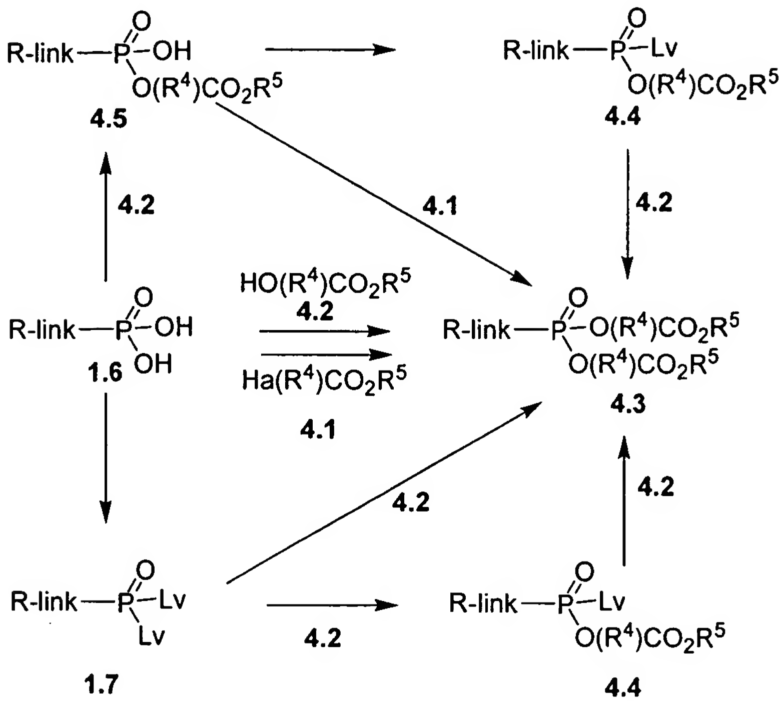
The methods are illustrated in Scheme **4**, Examples **3** and **4**. As shown in Example **3**, the phosphoryl dichloride **2.22** is reacted with three molar equivalents of ethyl 3-hydroxy-2-(hydroxymethyl)propionate **4.9** in tetrahydrofuran containing potassium carbonate, to obtain the diester product **4.10**.

Using the above procedure, but employing, in place of ethyl 3-hydroxy-2-(hydroxymethyl)propionate **4.9**, different hydroxyesters **4.2**, the corresponding products **4.3** are obtained.

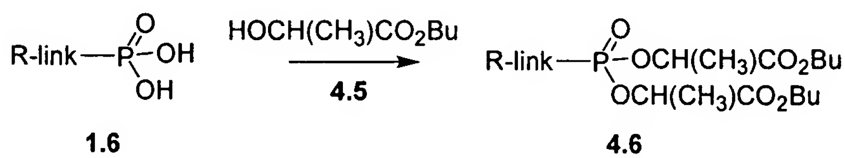
Scheme **4**, Example **4** depicts the displacement reaction between equimolar amounts of the phosphoryl dichloride **2.22** and ethyl 2-methyl-3-hydroxypropionate **4.11**, to yield the monoester product **4.12**. The reaction is conducted in acetonitrile at 70°C in the presence of diisopropylethylamine. The product **4.12** is then reacted, under the same conditions, with one molar equivalent of ethyl lactate **4.13**, to give the diester product **4.14**.

Using the above procedures, but employing, in place of ethyl 2-methyl-3-hydroxypropionate **4.11** and ethyl lactate **4.13**, sequential reactions with different hydroxyesters **4.2**, the corresponding products **4.3** are obtained.

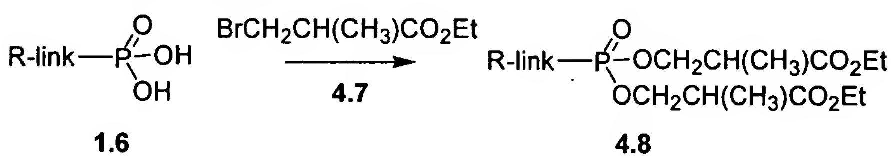
Scheme 4



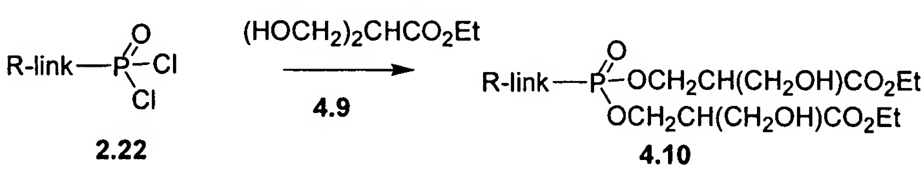
Scheme 4 Example 1



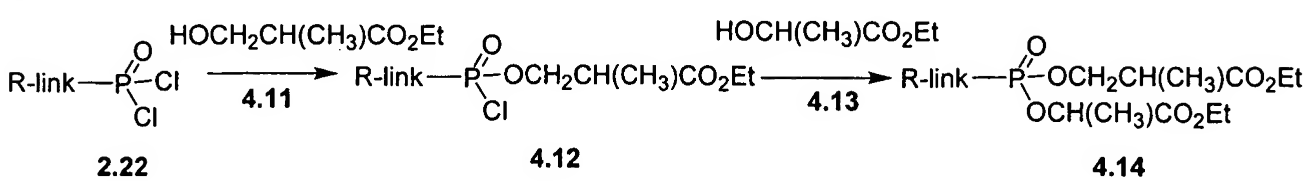
Scheme 4 Example 2



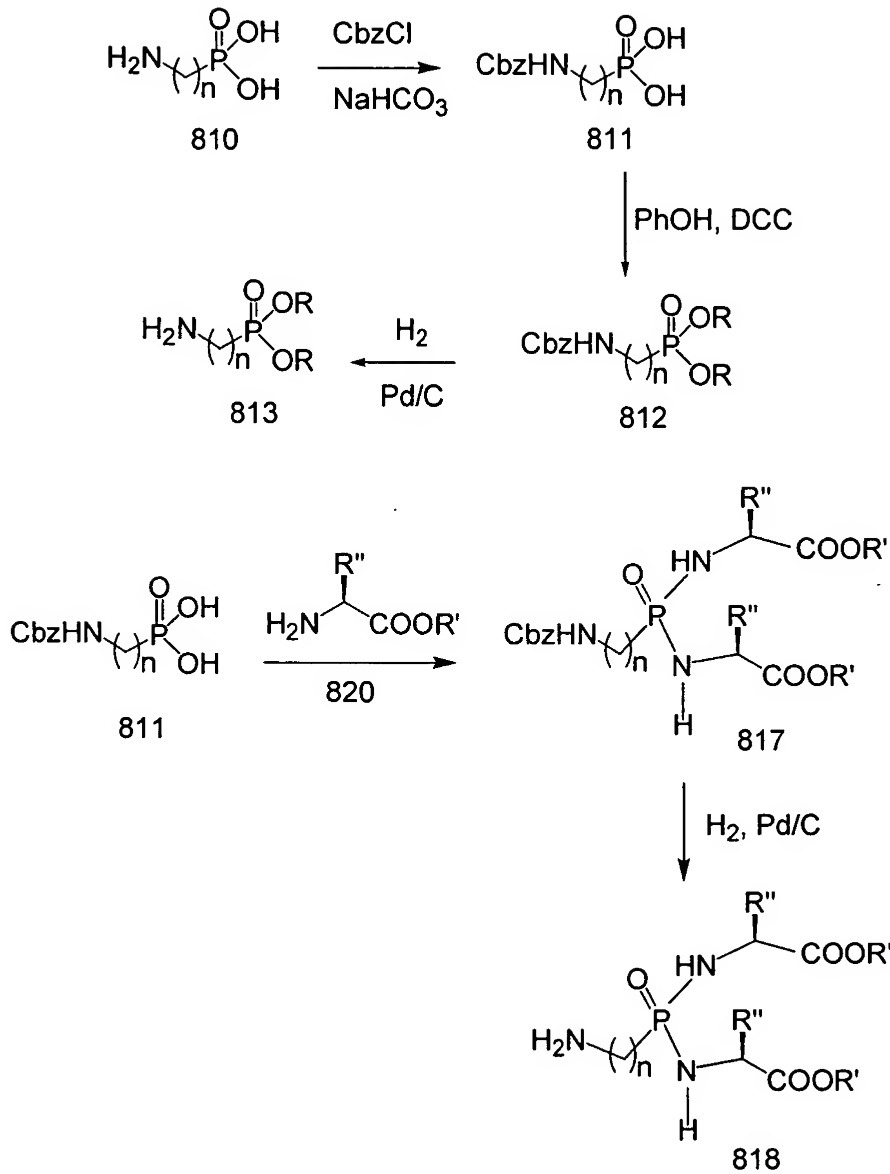
Scheme 4 Example 3

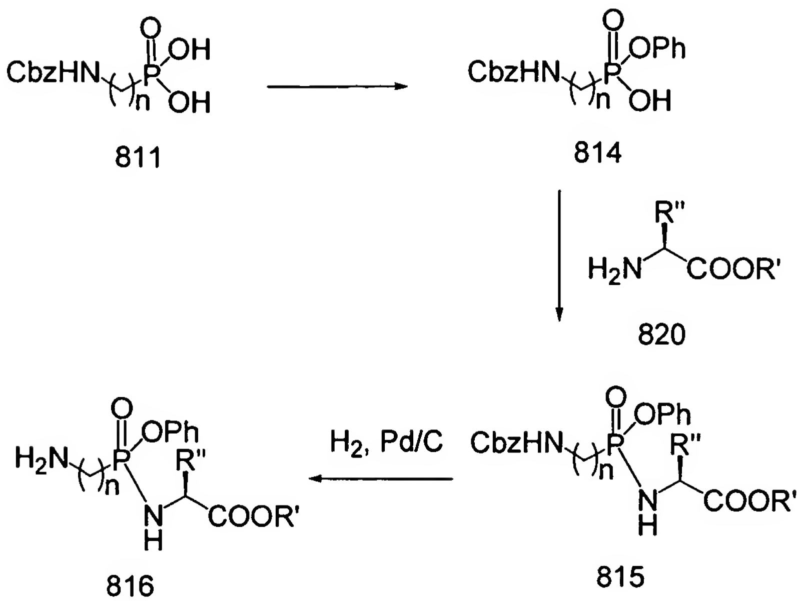


Scheme 4 Example 4



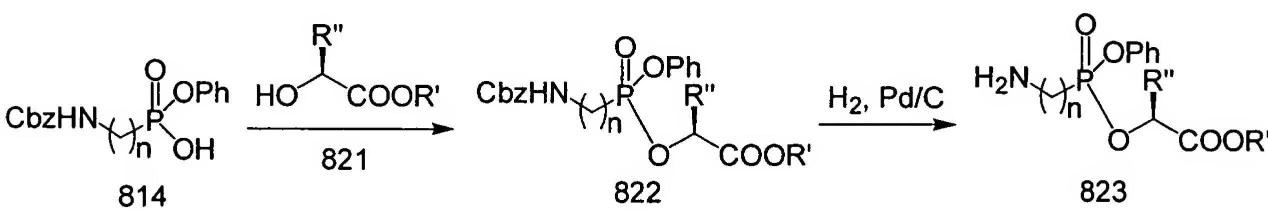
Scheme Y2



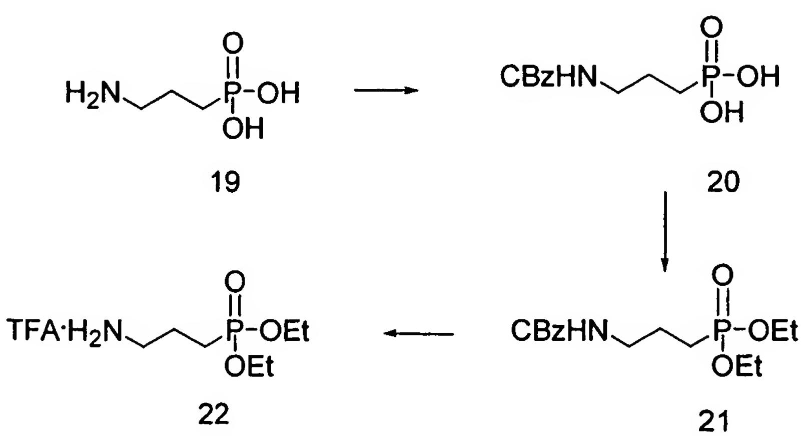


Following the similar procedures, replacement of amino acid esters 820 with lactates 821 (Scheme Y3) provides mono-phosphonic lactates 823. Lactates 823 are useful intermediates to form the phosphonate compounds of the invention.

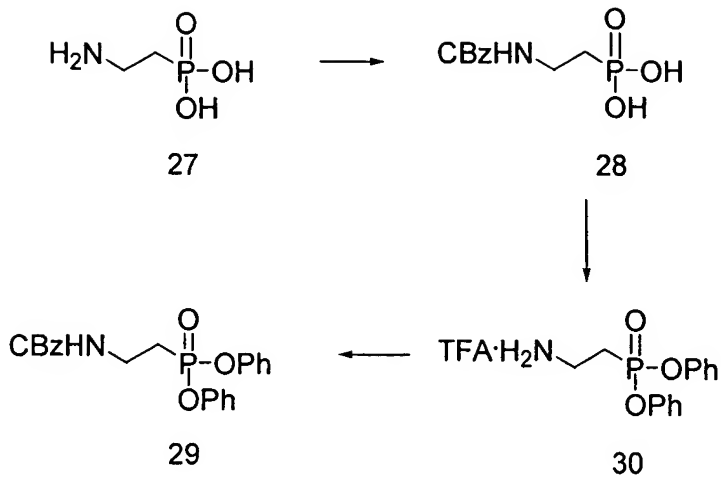
Scheme Y3



Scheme Y4



Scheme Y5



Example Y1

To a solution of 2-aminoethylphosphonic acid (1.26 g, 10.1 mmol) in 2N NaOH (10.1 mL, 20.2 mmol) was added benzyl chloroformate (1.7 mL, 12.1 mmol). After the reaction mixture was stirred for 2 d at room temperature, the mixture was partitioned between Et_2O and water. The aqueous phase was acidified with 6N HCl until pH = 2. The resulting colorless solid was dissolved in MeOH (75 mL) and treated with Dowex 50WX8-200 (7 g). After the mixture was stirred for 30 minutes, it was filtered and evaporated under reduced pressure to give carbamate **28** (2.37 g, 91%) as a colorless solid (Scheme Y5).

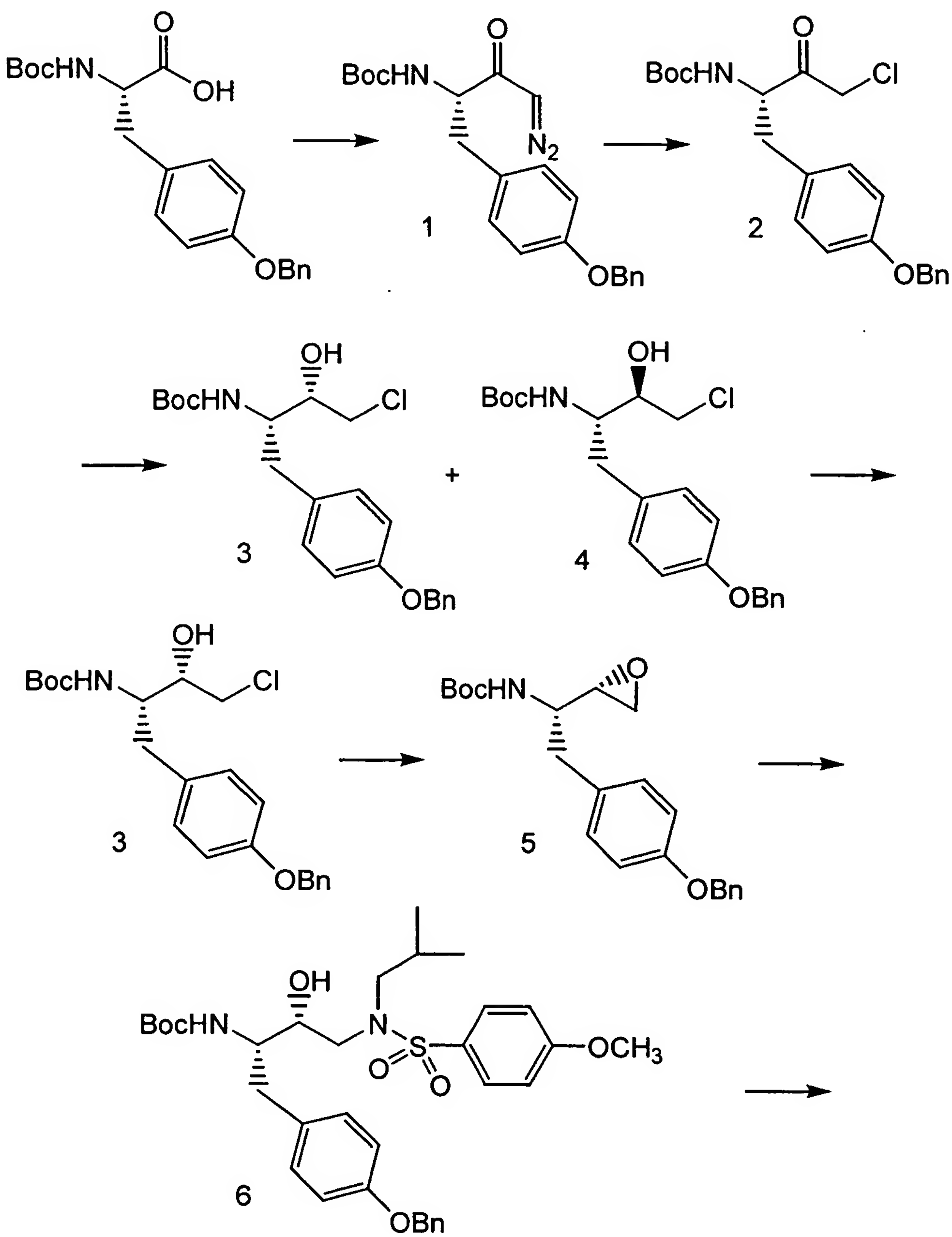
To a solution of carbamate **28** (2.35 g, 9.1 mmol) in pyridine (40 mL) was added phenol (8.53 g, 90.6 mmol) and 1,3-dicyclohexylcarbodiimide (7.47 g, 36.2 mmol). After the reaction mixture was warmed to 70°C and stirred for 5 h, the mixture was diluted with CH_3CN and filtered. The filtrate was concentrated under reduced pressure and diluted with EtOAc. The organic phase was washed with sat. NH_4Cl, sat. $NaHCO_3$, and brine, then dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel twice (eluting 40-60% EtOAc/hexane) to give phosphonate **29** (2.13 g, 57%) as a colorless solid.

To a solution of phosphonate **29** (262 mg, 0.637 mmol) in iPrOH (5 mL) was added TFA (0.05 mL, 0.637 mmol) and 10% Pd/C (26 mg). After the reaction mixture was stirred under H_2 atmosphere (balloon) for 1 h, the mixture was filtered through Celite. The filtrate was evaporated under reduced pressure to give amine **30** (249 mg, 100%) as a colorless oil (Scheme Y5).

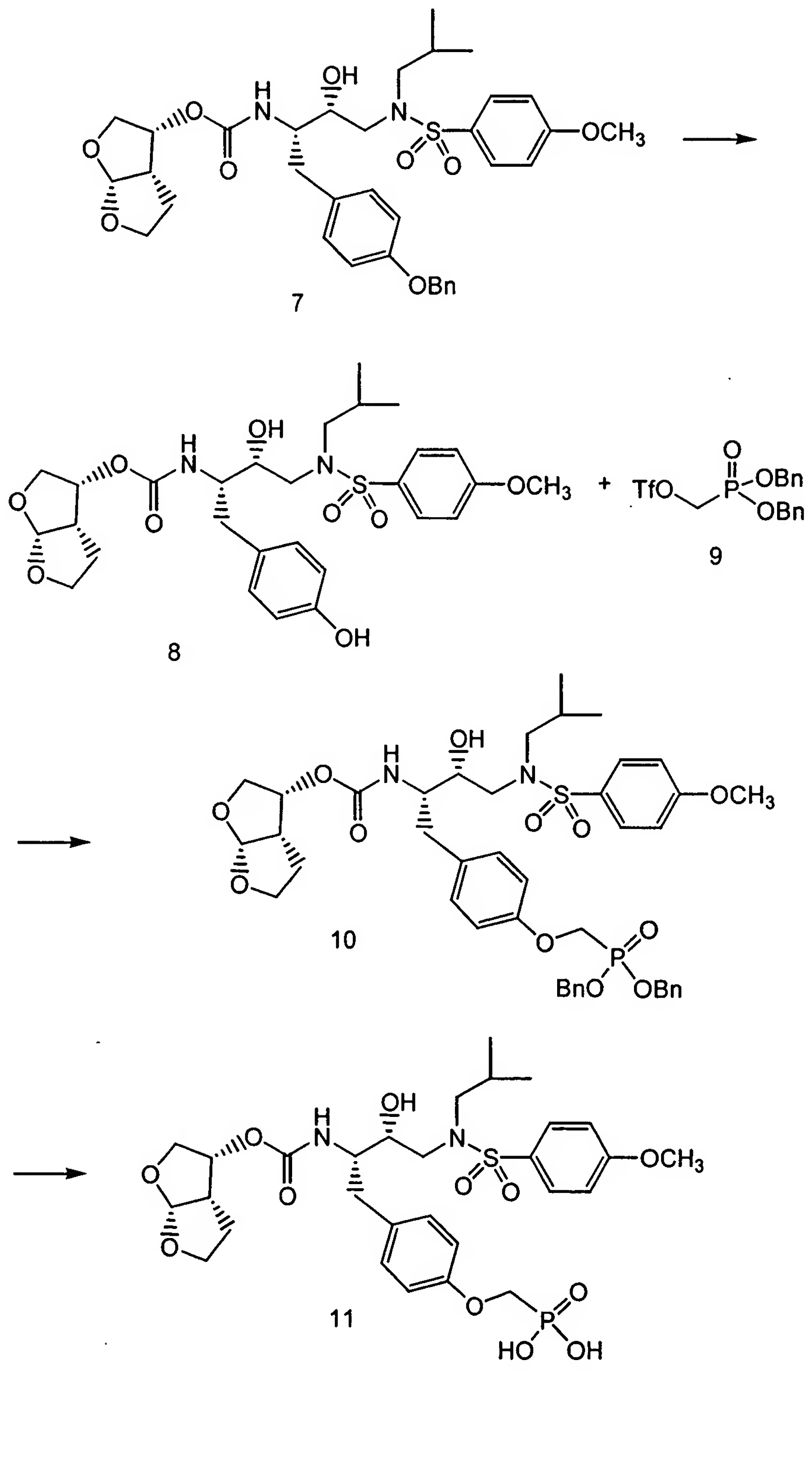
Scheme Section A

Exemplary methods of preparing the compounds of the invention are shown in **Schemes A1-A7** below. A detailed description of the methods is found in the Experimental section below.

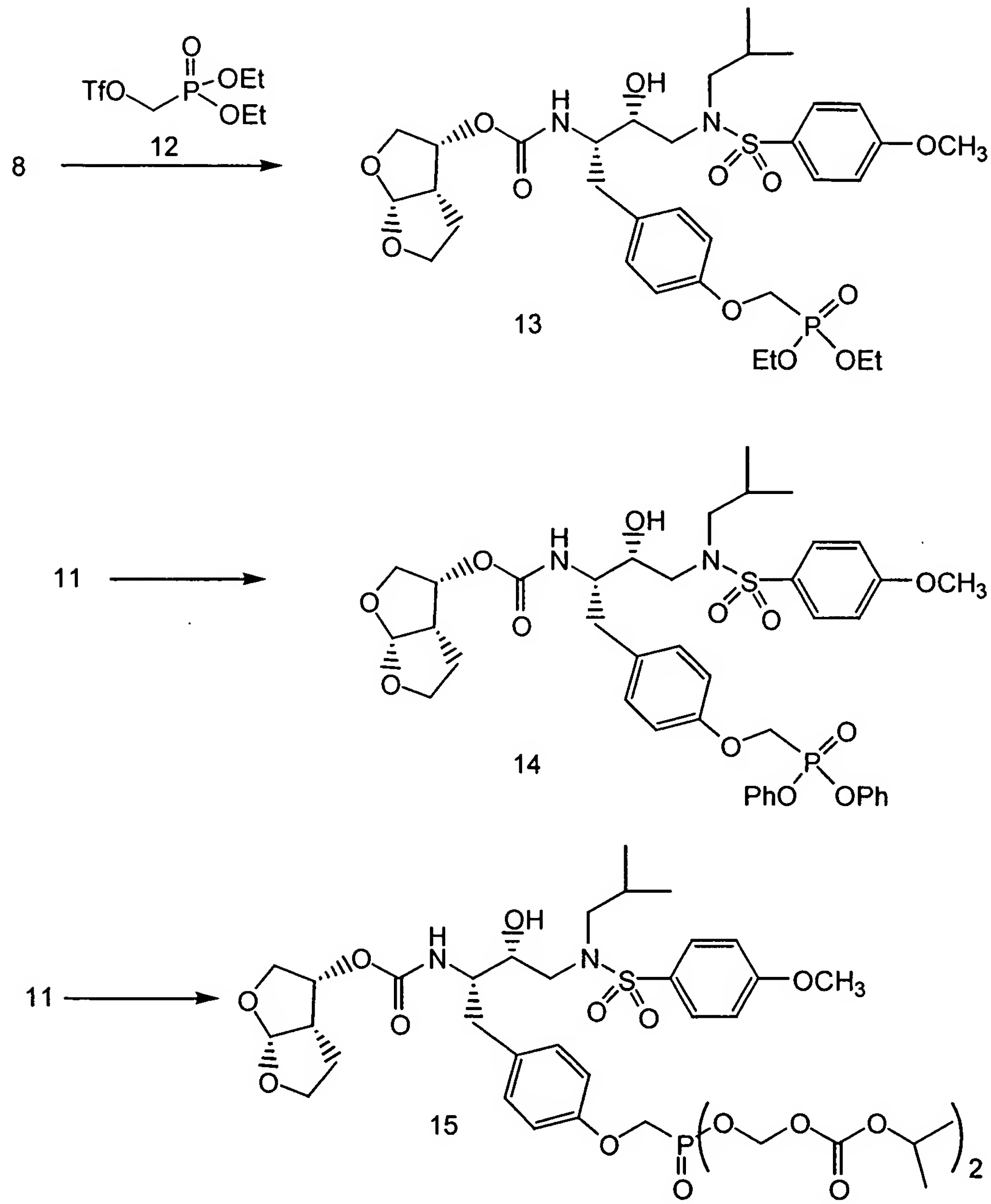
Scheme A1



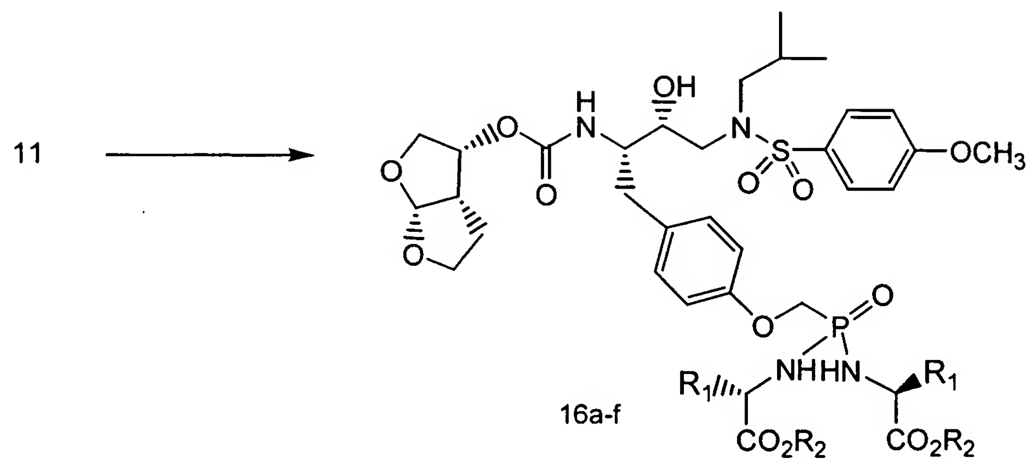
Scheme A2



Scheme A3

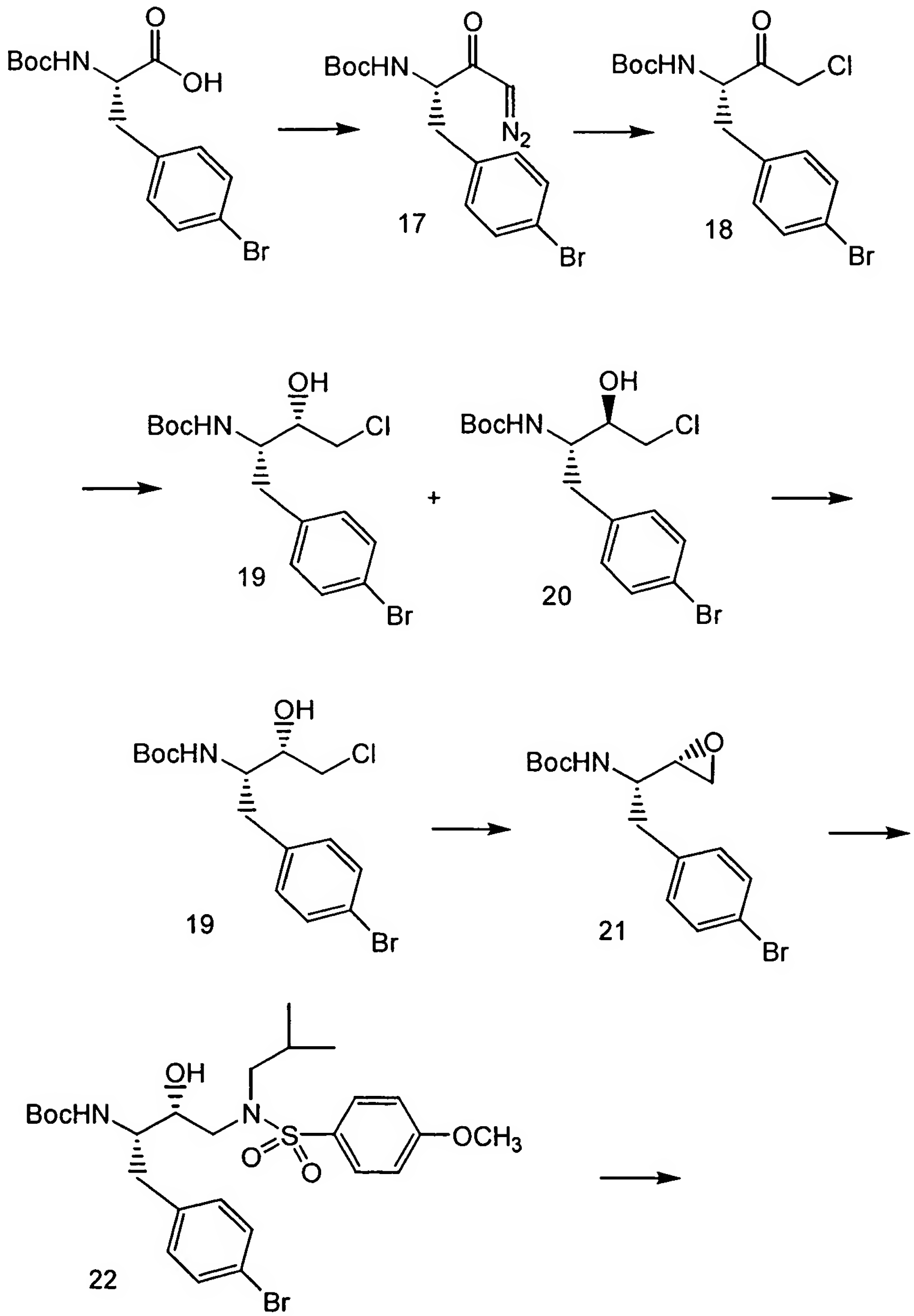


Scheme A4

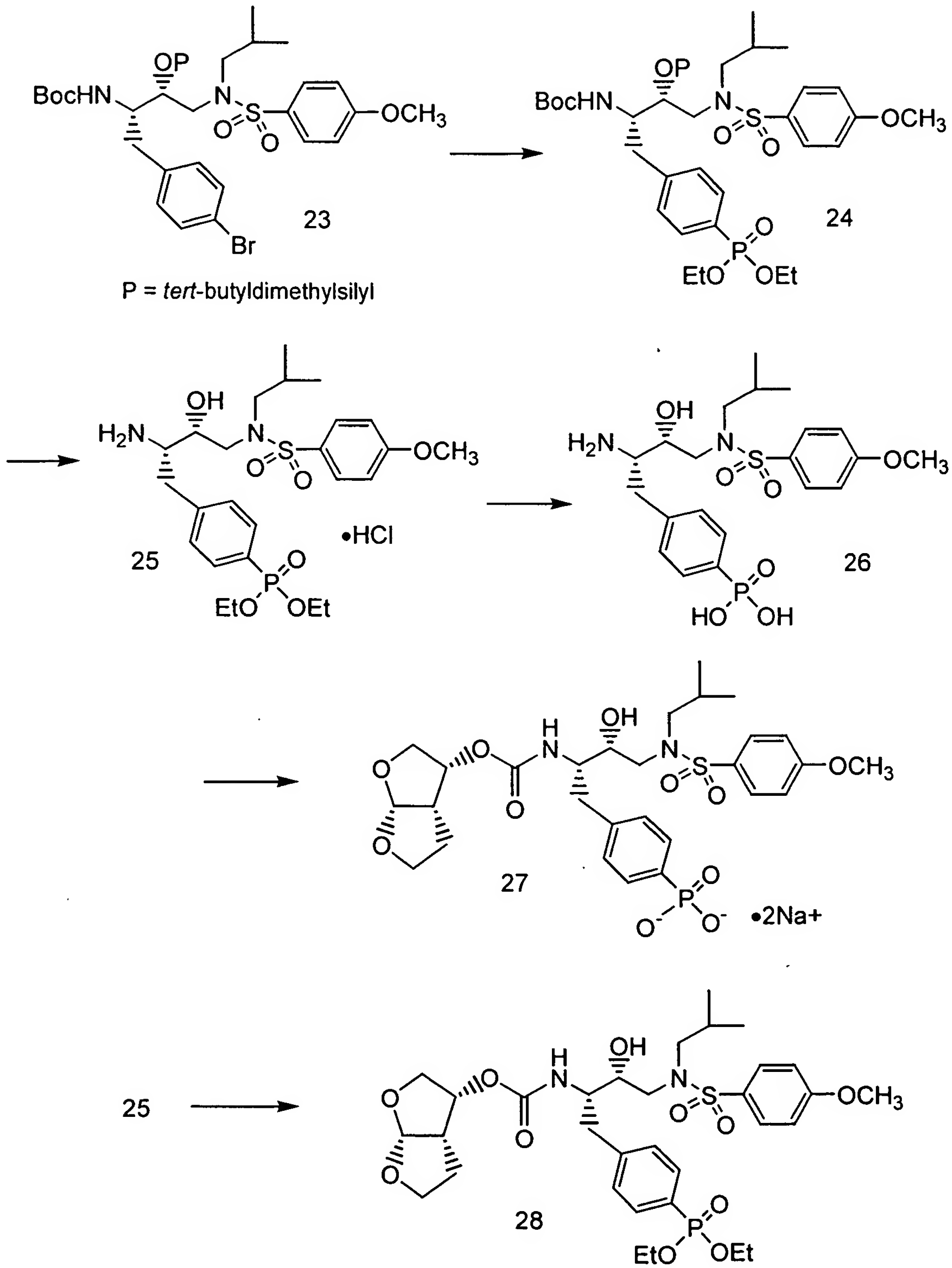


16a-f

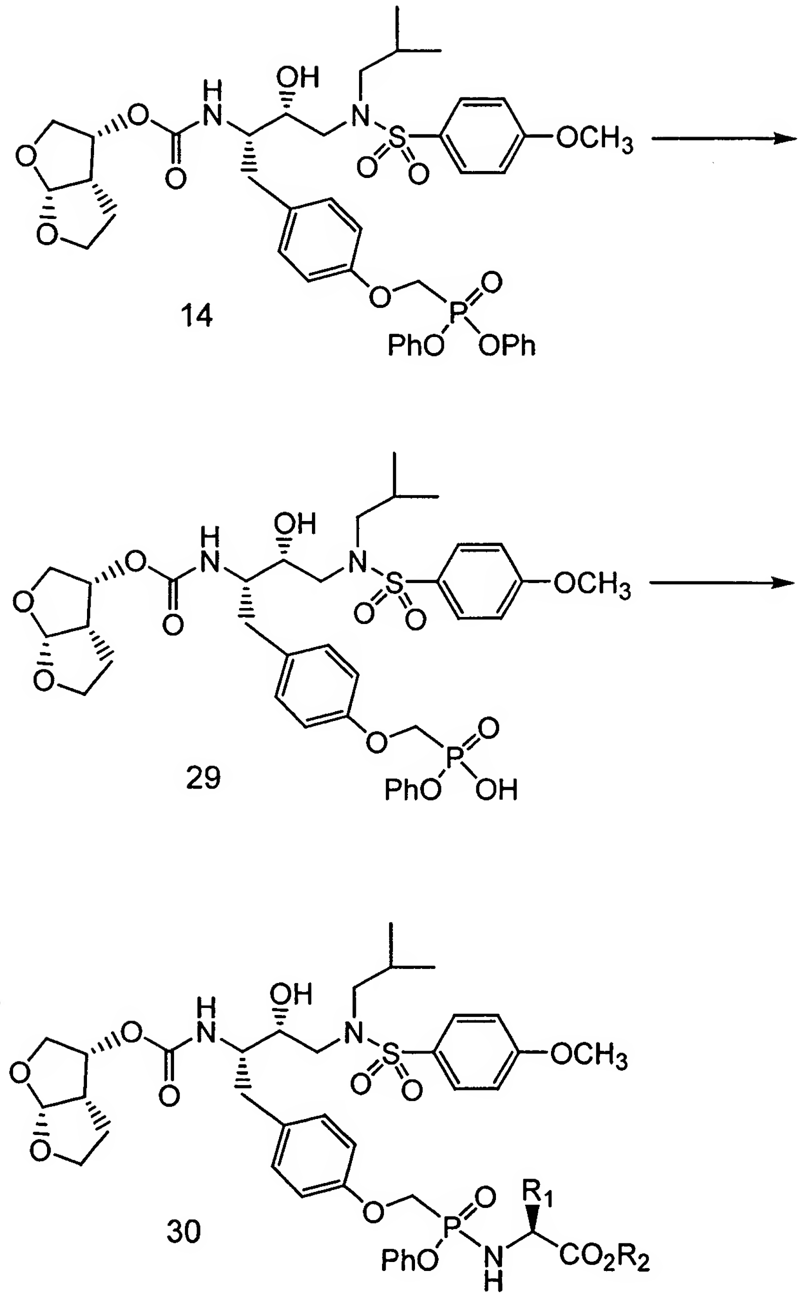
Scheme A5



Scheme A6



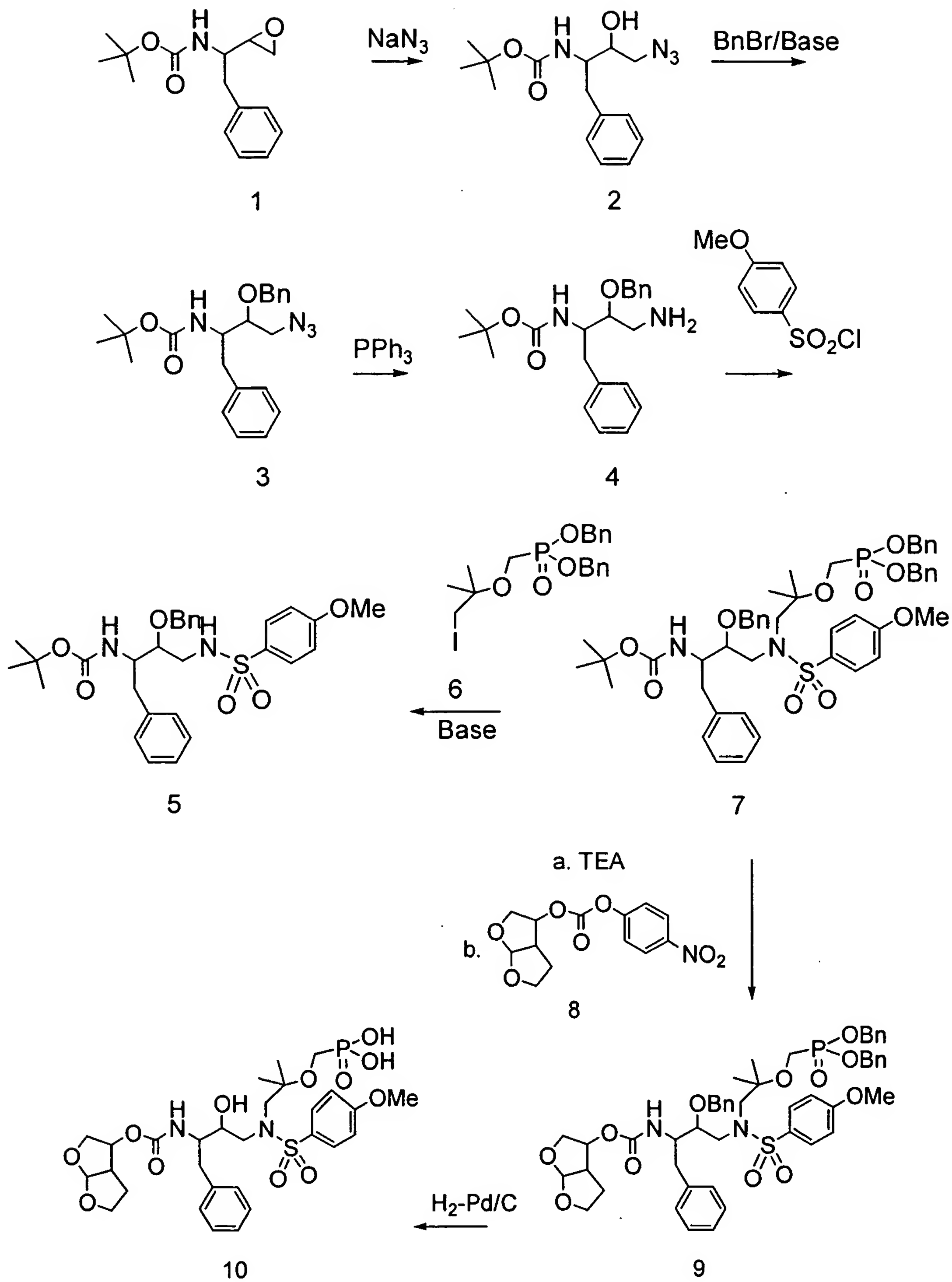
Scheme A7



Scheme Section B

Alternative exemplary methods of preparing the compounds of the invention are shown in **Schemes B1-B13** below.

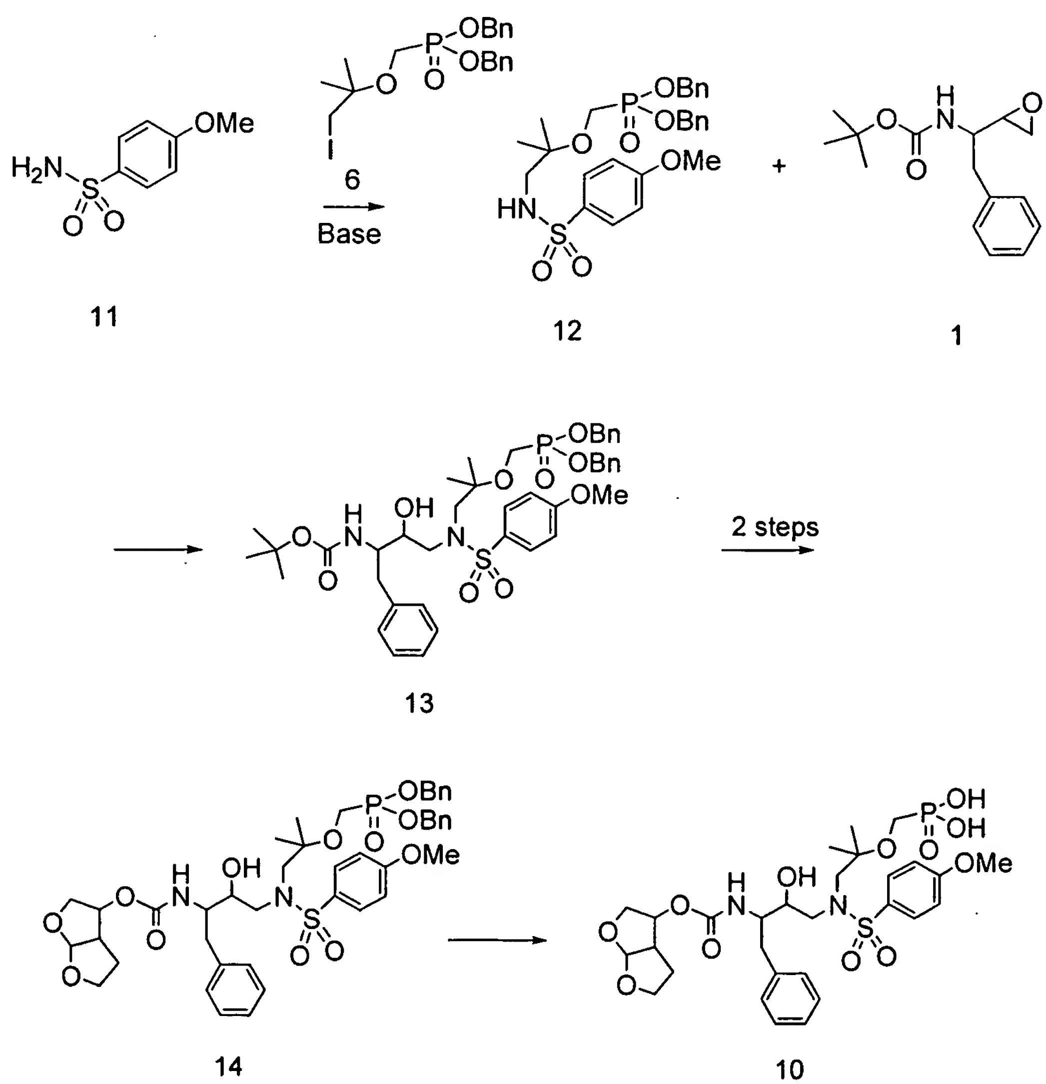
Scheme B1



Treatment of commercially available epoxide 1 with sodum azide (*Bioorg. & Med. Chem. Lett.*, 5, 459, 1995) furnishes the azide intermediate 2. The free hydroxyl is converted to benzyl ether 3 by treating it with benzyl bromide in the presence of base such as potassium

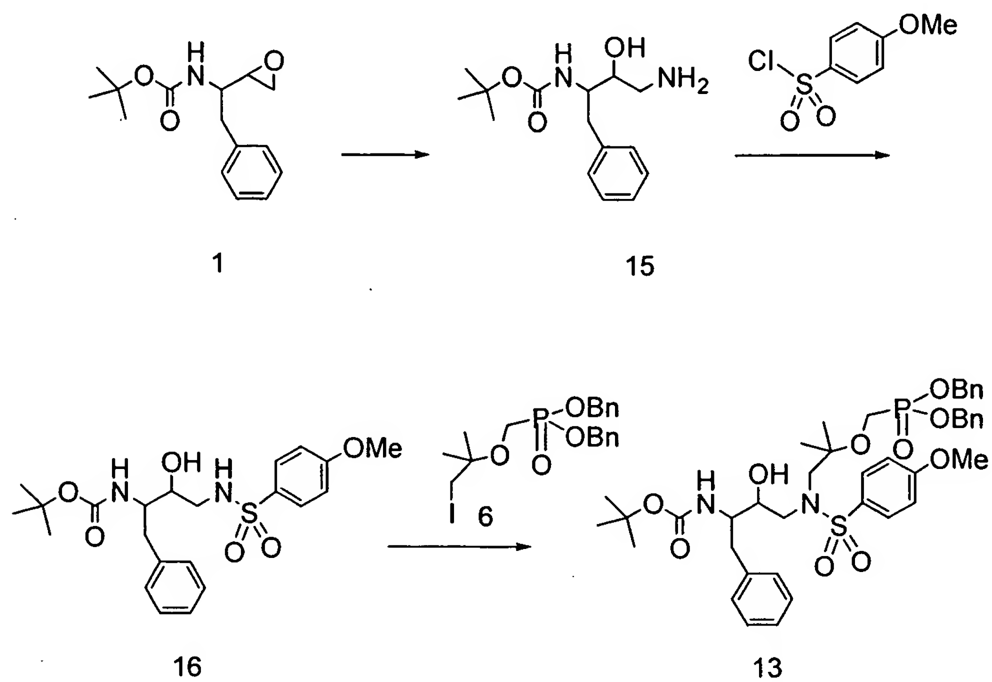
carbonate. Compound 4 is achieved by the reduction of the azide group with triphenyl phosphine, as described in the publication *Bioorg. & Med. Chem. Lett.*, 7, 1847, 1997. Conversion of the amino group to its sulfonamide derivative 5 is achieved by treating the amine with stoichiometric amounts of sulfonyl chloride. Regioselective alkylation is performed (as shown in the article *J. Med. Chem.*, 40, 2525, 1997) on the sulfonamide nitrogen using the iodide 6 (*J. Med. Chem.*, 35, 2958, 1992) to get the compound 7. Upon TFA catalyzed deprotection of BOC group followed by the reaction with bisfuranyl carbonate 8 (for a similar coupling see, *J. Med. Chem.*, 39, 3278, 1996) furnishes the compound 9. Final deprotection of the protecting groups by catalytic hydrogenolysis result the compound 10.

Scheme B2



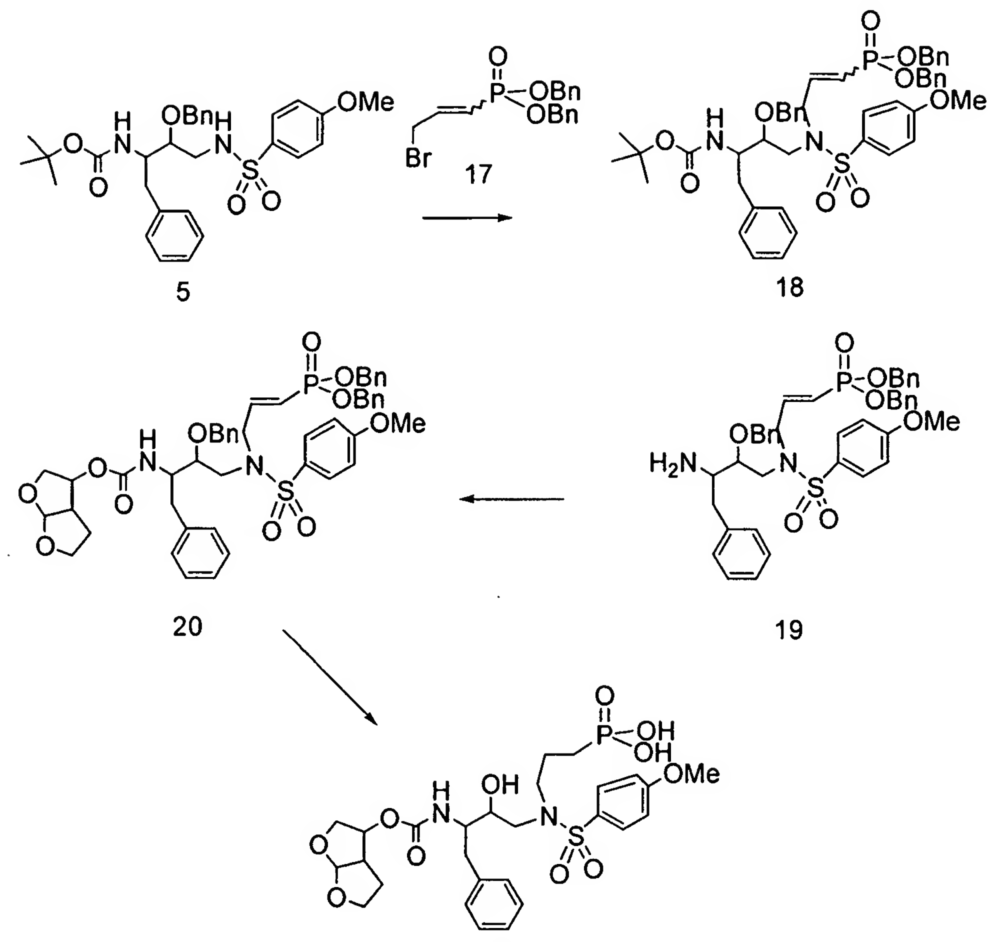
The sulfonamide 11 is readily alkylated with the iodide 6 (*J. Med. Chem.*, 35, 2958, 1992) to get the intermediate 12. Regioselective epoxide opening (JP -9124630) of the epoxide 1 with 12 furnishes the intermediate 13. Deprotection of the BOC group followed by the treatment of bisfuranyl carbonate 8 yields the intermediate 14 which is subjected to hydrogenation to furnish the compound 10.

Scheme B3



The epoxide 1 is converted to the aminohydroxyl derivative 15 using the known procedure (*J. Med. Chem.*, 37, 1758, 1994). Sulfonylation of 15 using benzene sulfonylchloride affords the compound 16. Installation of the side chain to get the intermediate 13 is achieved by alkylation of sulfonamide nitrogen with iodide 6. The intermediate 13 is converted to the compound 10 using the same sequence as shown in scheme B2.

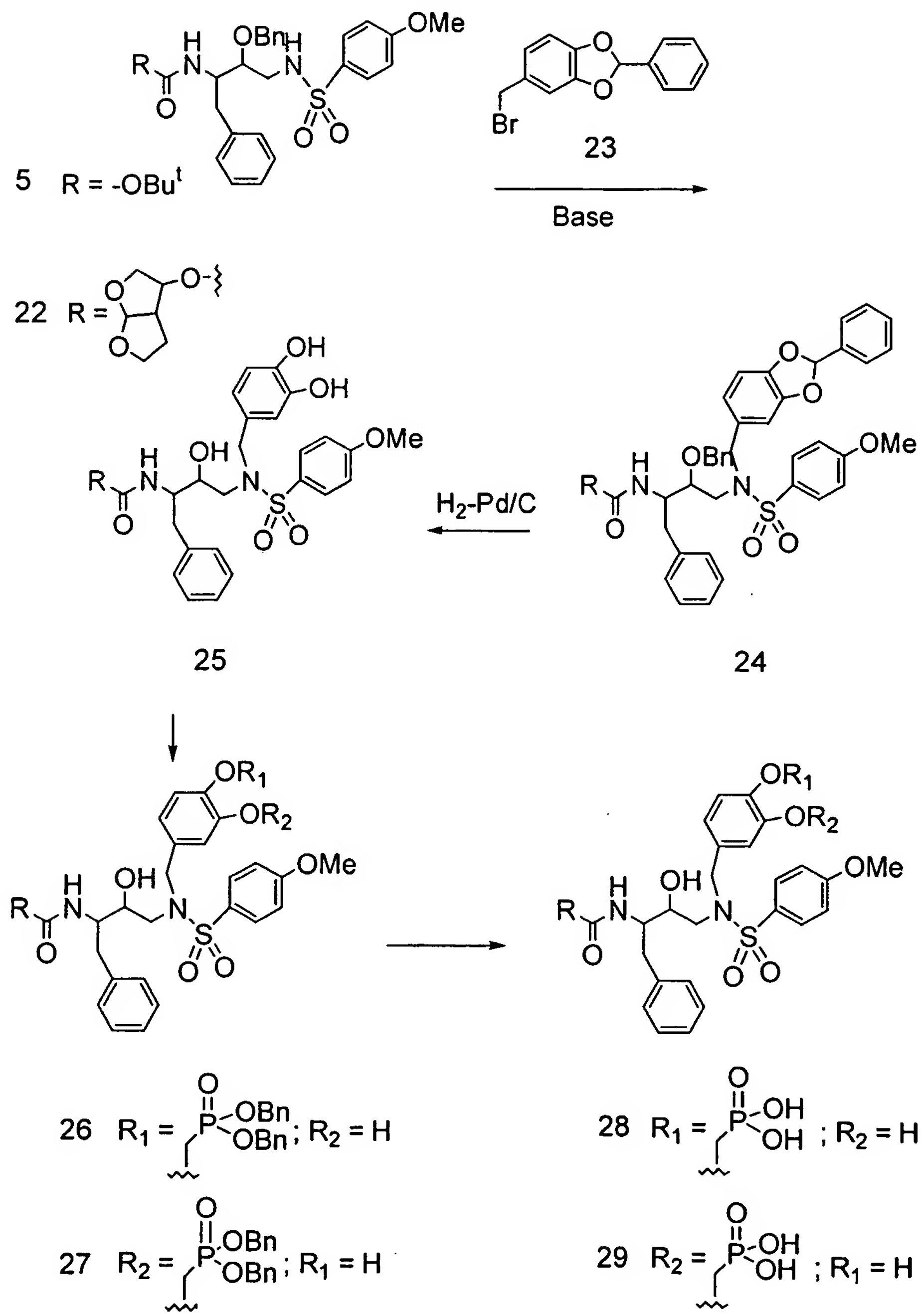
Scheme B4



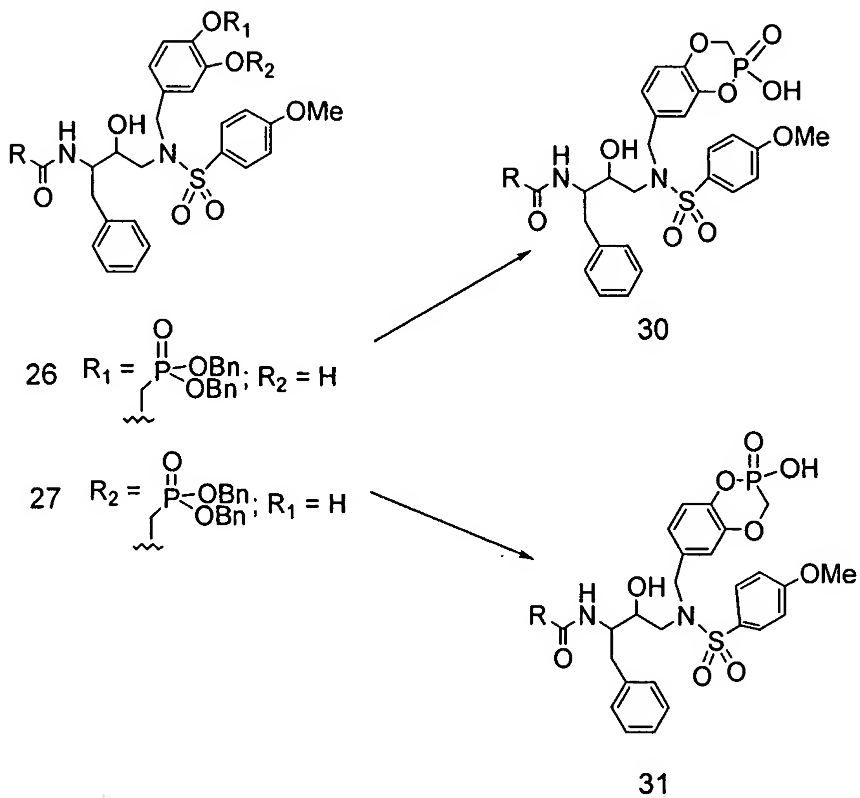
21

Sulfonamide 5 is alkylated under basic conditions using the allyl bromide 17 (*Chem. Pharm. Bull.*, 30, 111, 1982) to get the intermediate 18. Similar transformation is reported in literature (*J. Med. Chem.*, 40, 2525, 1997). Hydrolysis of BOC group with TFA and acylation of the resulting amine 19 with bisfuranyl carbonate 8 yields the compound 20. Hydrogenation using Pd/C catalysis under H_2 atmosphere affords the phosphonic acid 21.

Scheme B5


5 R = -OBu^t
22 R =
23
Base
H_2-Pd/C
24
25
26 R_1 = ; R_2 = H
27 R_2 = ; R_1 = H
28 R_1 = ; R_2 = H
29 R_2 = ; R_1 = H

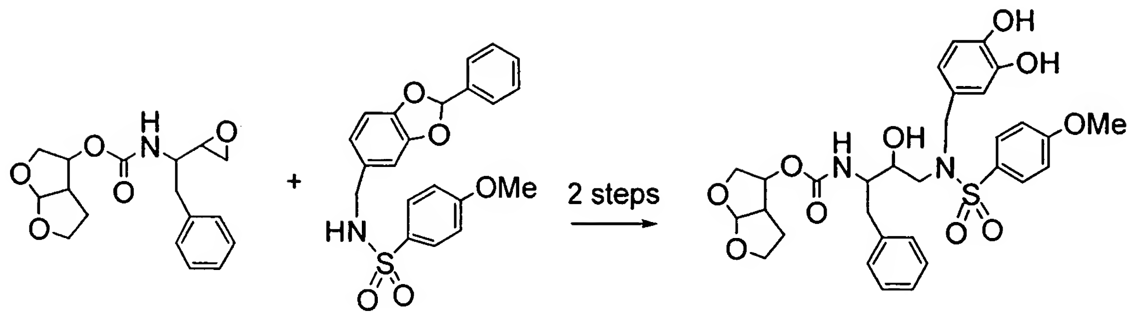
Scheme B5 (cont'd)



Sulfonamide 5 is converted to 22 via hydrolysis of BOC group with TFA and acylation with bisfuranyl carbonate 8. The sulfonamide 22 is alkylated with the bromide 23 (*J. Med. Chem.*, 40, 2525, 1997) to get the compound 24, which upon hydrogenolysis gives the catechol 25. Alkylation of the phenolic groups using dibenzylhydroxymethyl phosphonate (*J. Org. Chem.*, 53, 3457, 1988) affords regioisomeric compounds 26 and 27. These compounds 26 and 27 are hydrogenated to get the phophonic acids 28 and 29, respectively. Individual cyclic phosphonic acids 30 and 31 are obtained under basic (like NaH) conditions (US 5886179) followed by hydrogenolysis of the dibenzyl ester derivatives 26 and 27.

Scheme B6

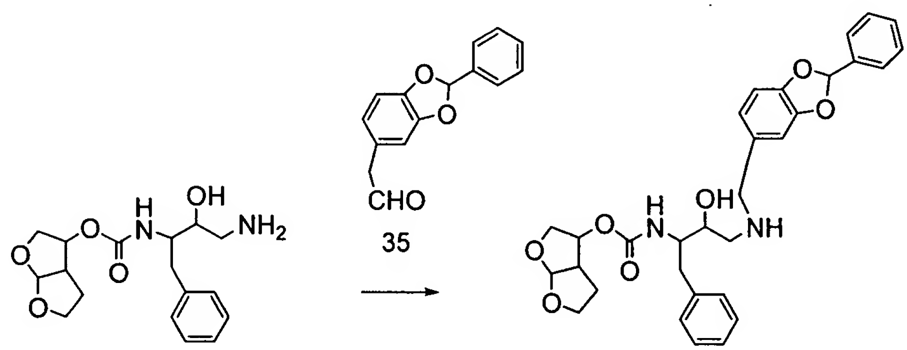
In this route, compound 25 is obtained by conducting a reaction between the epoxide 32 and the sulfonamide 33 using the conditions described in the Japanese Patent No. 9124630.



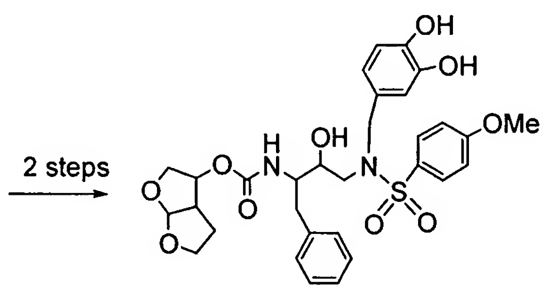
32 33 25

Epoxide 32 and sulfonamide 33 are synthesized utilizing similar methodology delineated in the same patent.

Scheme B7



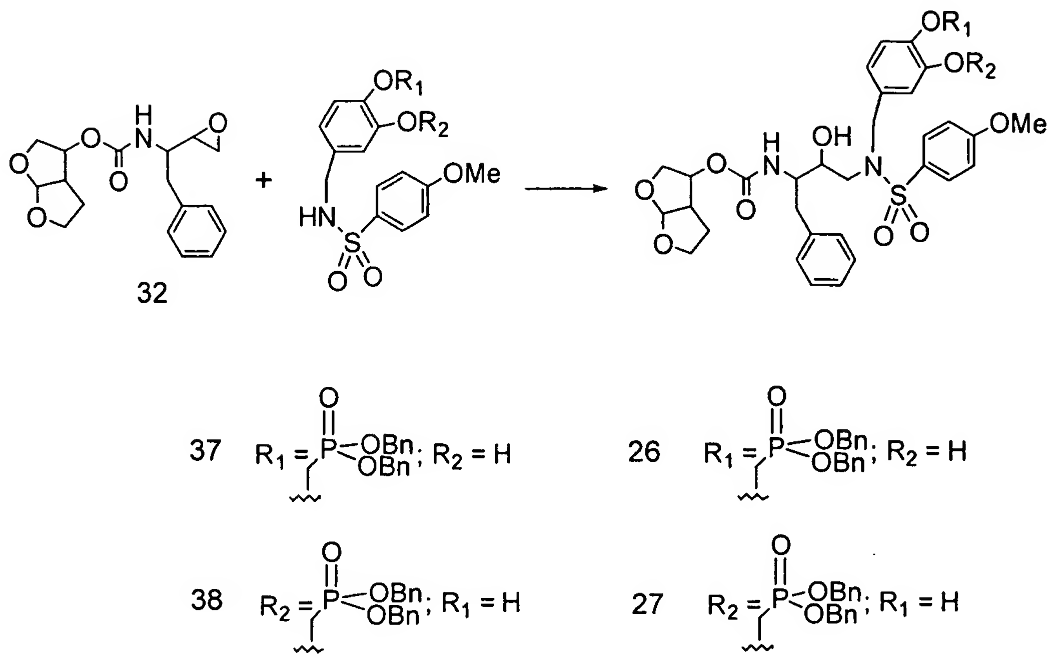
34 36



25

Compound 34 is obtained from 32 using similar sequence depicted in *J. Med. Chem.*, 37, 1758, 1994. Reductive amination (for similar transformation see WO 00/47551) of compound 34 with aldehyde 35 furnishes the intermediate 36 which is converted to the compound 25 by sulfonylation followed by hydrogenation.

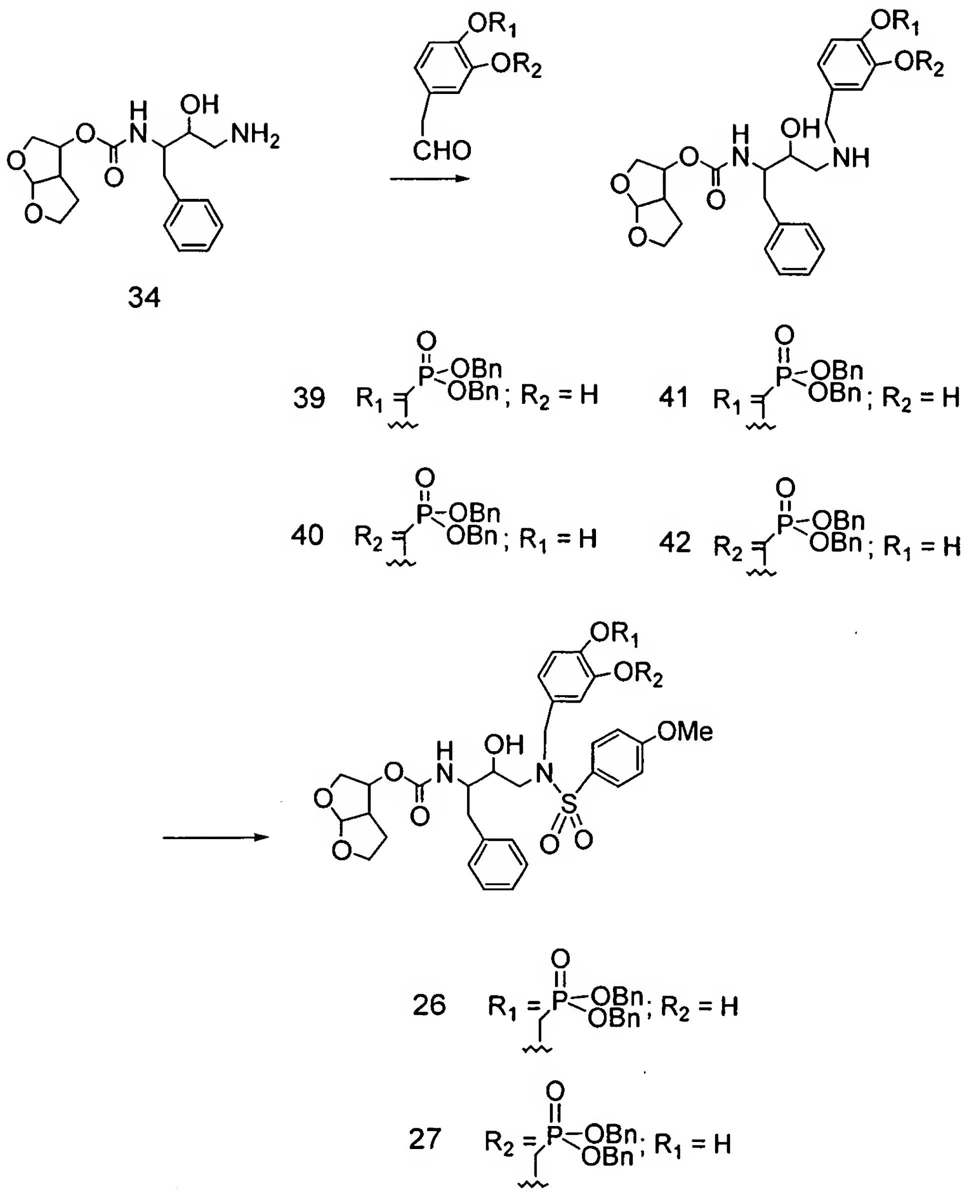
Scheme B8



Treatment of epoxide 32 with sulfonamides 37 and/or 38 under conditions described in Japanese Patent No. 9124630 furnishes 26 and 27.

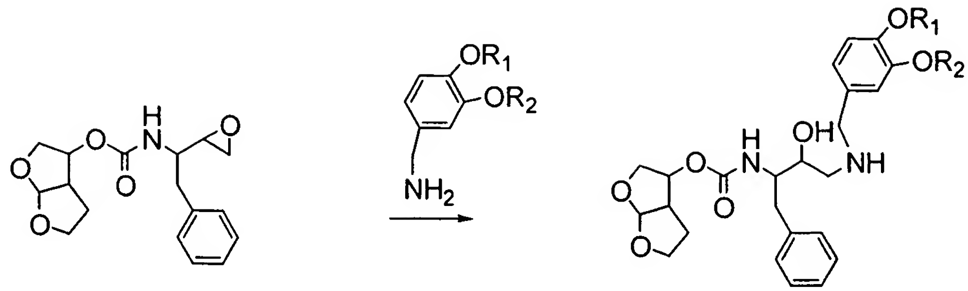
Scheme B9

Reductive amination of aminohydroxyl intermediate 34 with the aldehydes 39 and 40 as described in patent WO 00/47551, furnish 41 and 42 which undergoes smooth sulfonylation to give 26 and 27.

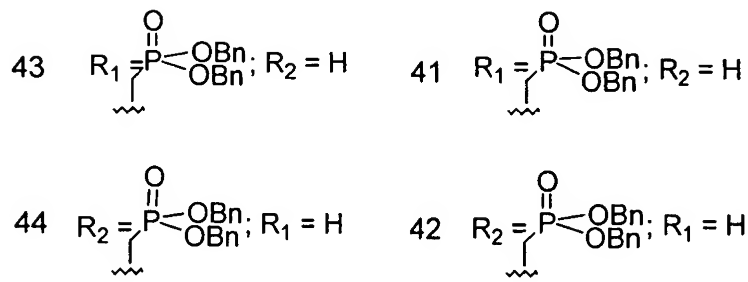


Scheme B10

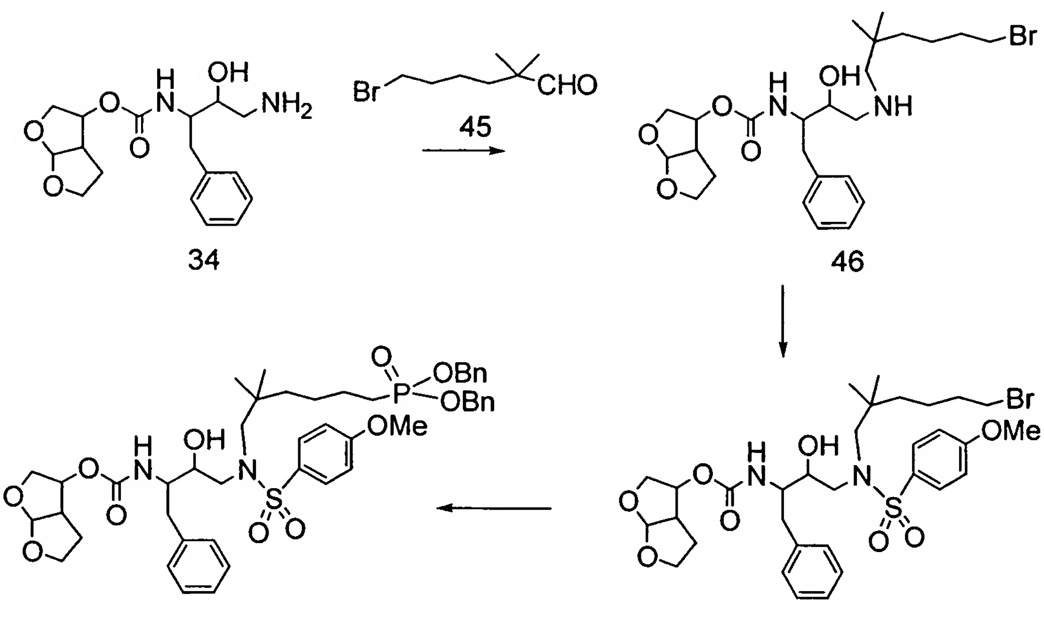
In an alternate approach, where epoxide 32 is opened with benzyl amines 43 and 44 under conditions described above furnishes 41 and 42, respectively. Similar transformations were documented in the Japanese Patent No. 9124630.

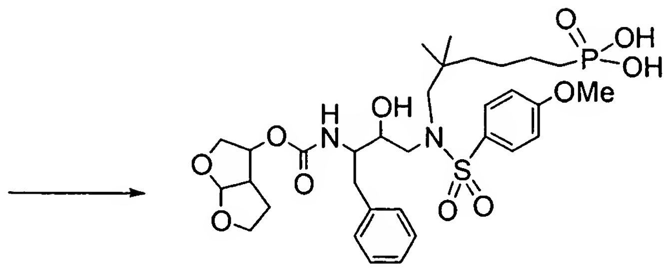


32



Scheme B11

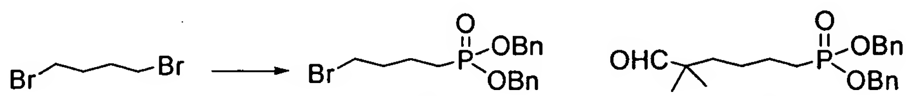




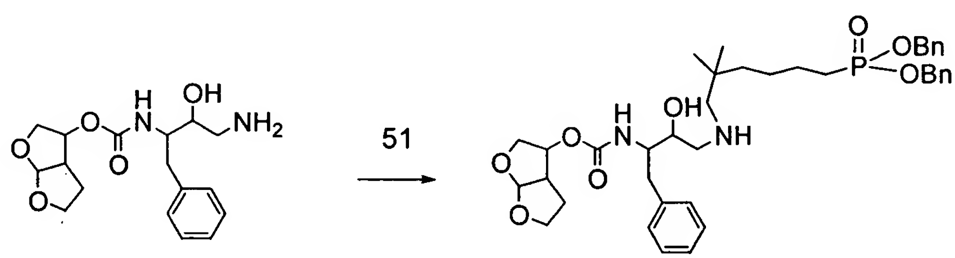
49

Reductive amination of the bromoaldehyde 45 (*J. Organomet. Chem.*, FR; 122, 123, 1976) with the amine 34 gives 46 which then undergoes sulfonylation to furnish 47. The bromoderivative 47 is converted to the phosphonate 48 under Michaelis-Arbuzov reaction conditions (*Bioorg. Med. Chem. Lett.*, 9, 3069, 1999). Final hydrogenation of 48 delivers the phosphonic acid 49.

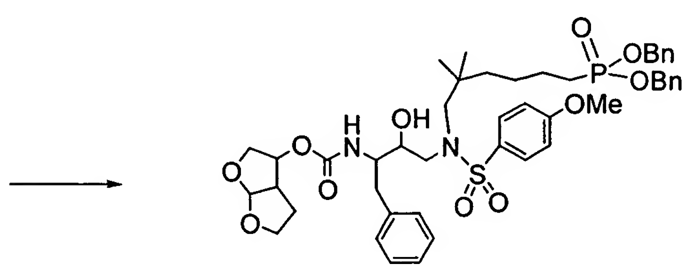
Scheme B12



50 51



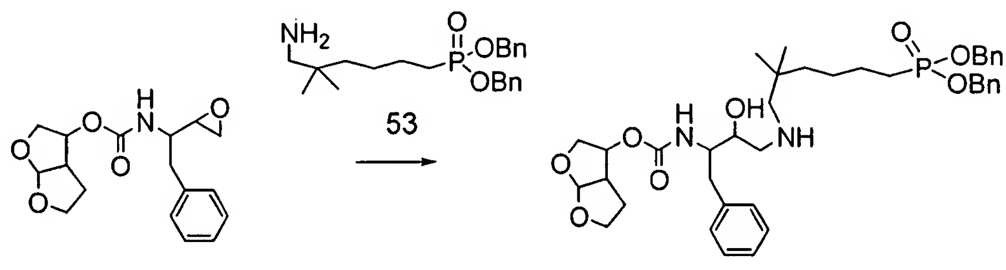
34 52



48

The intermediate 48 is also obtained as shown in scheme 112. Reductive amination of the aldehyde 52 with the amine 34 offers the phosphonate 52 and sulfonylation of this intermediate furnishes 48.

Scheme B13



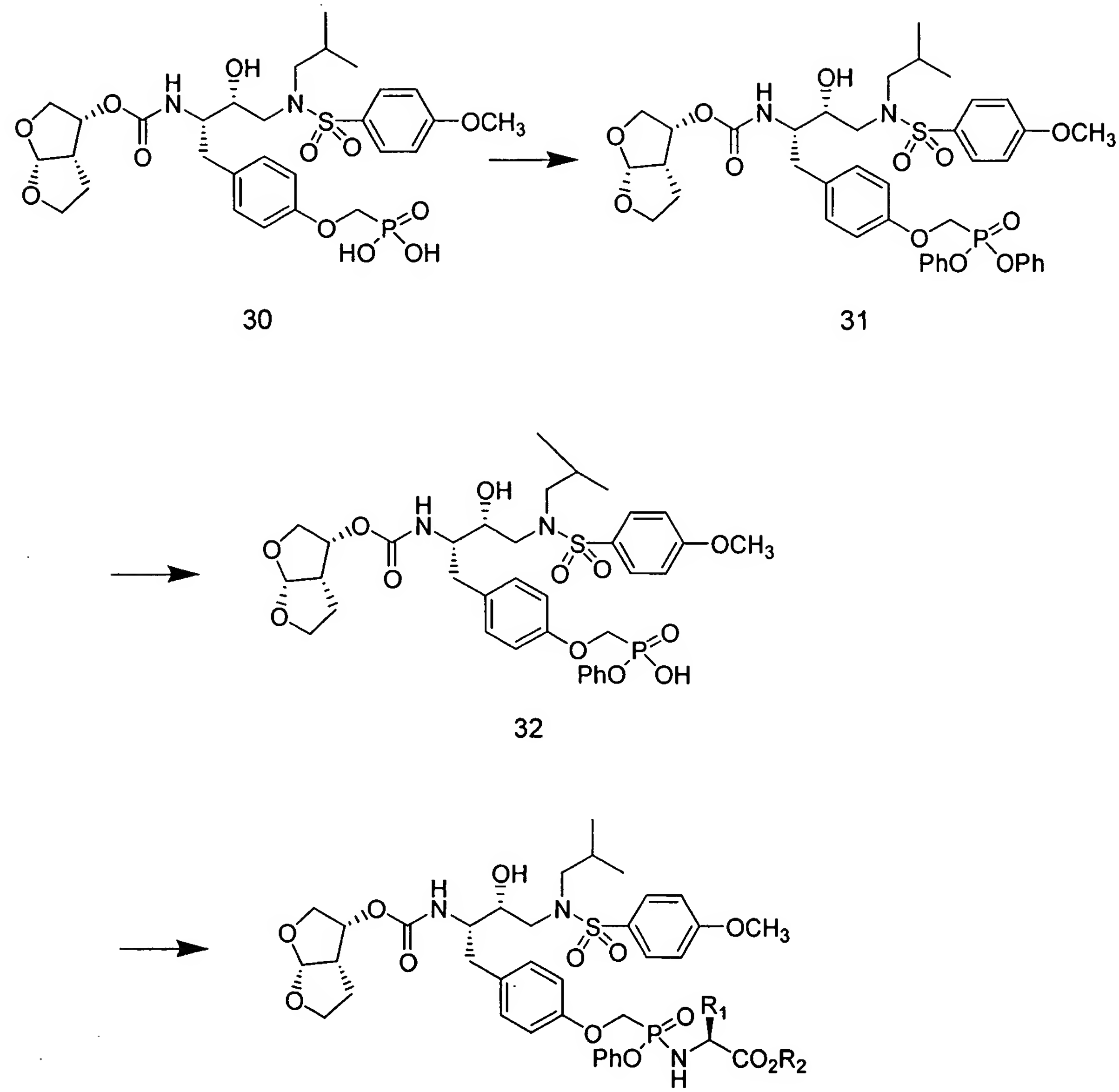
32 52

Alternatively, compound 52 is obtained from the epoxide 32 by a ring opening reaction with the aminophosphonate 53 (Scheme B13).

Scheme Section C

Scheme C1 is described in the Examples.

Scheme C1

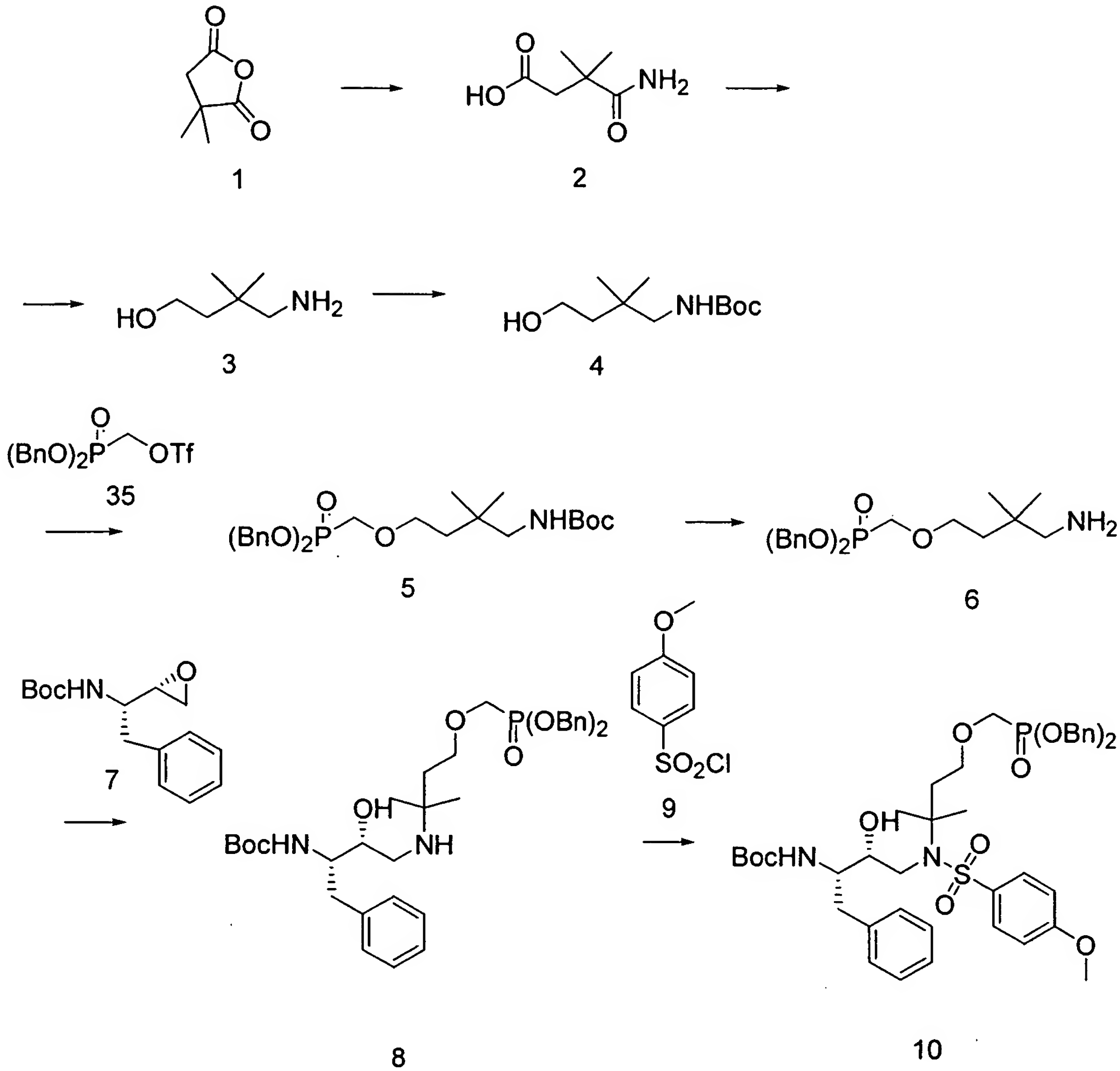


33

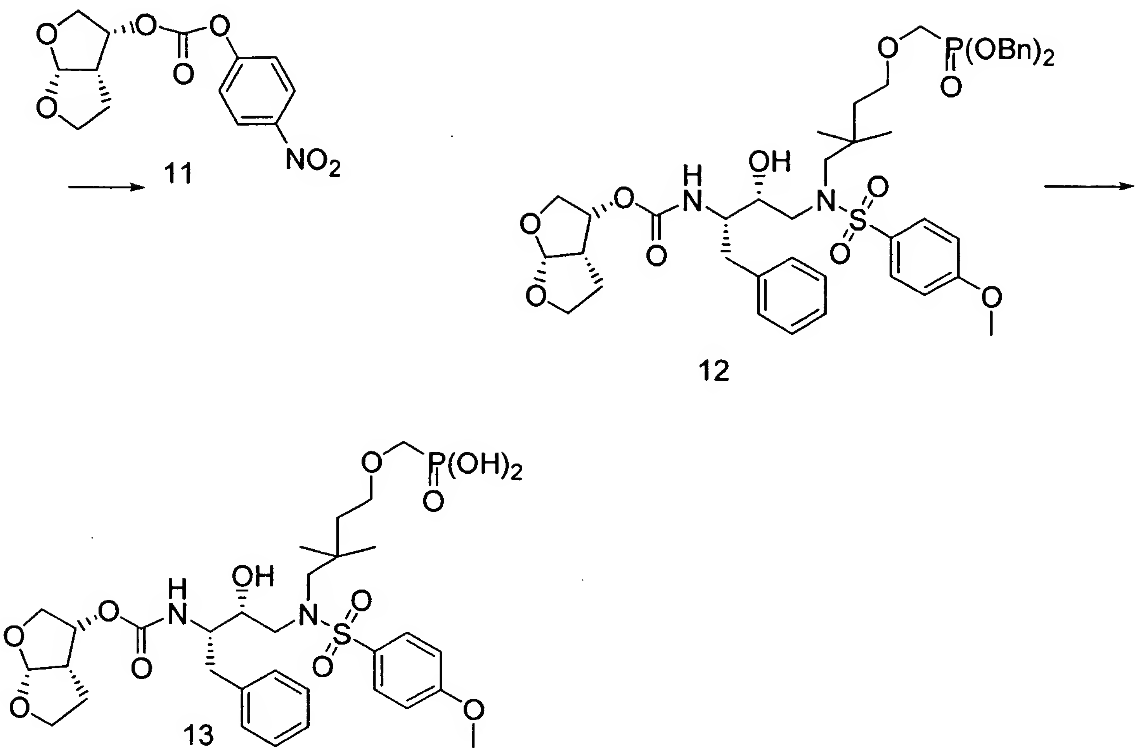
Scheme Section D

The following schemes are described in the Examples.

Scheme D1

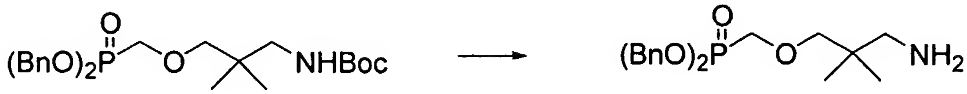


Scheme D1 (cont'd)

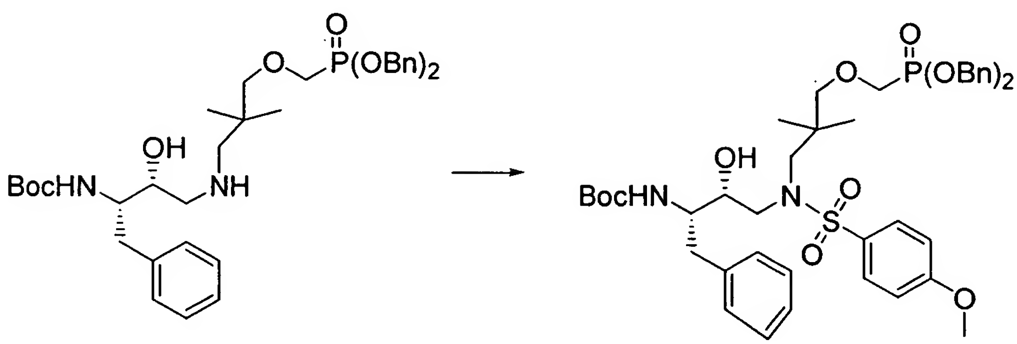


Scheme D2

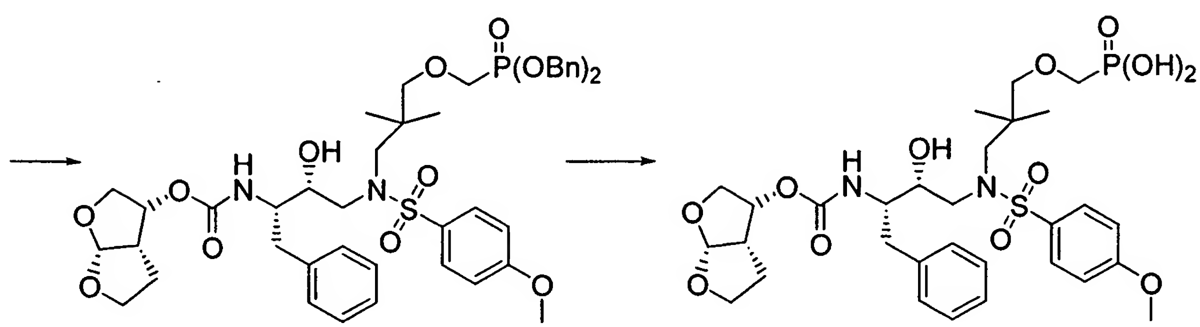
14 15



16 17

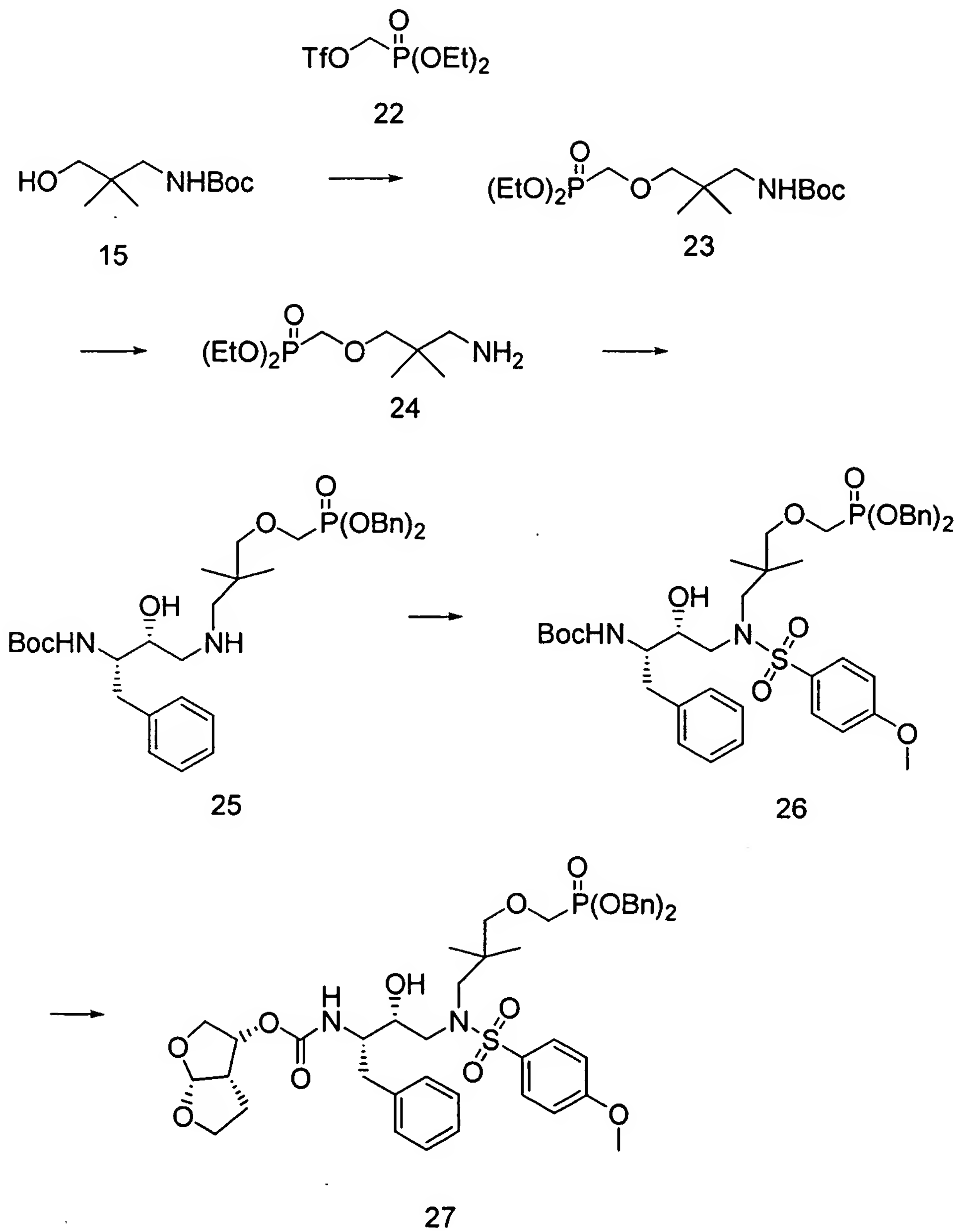


18 19

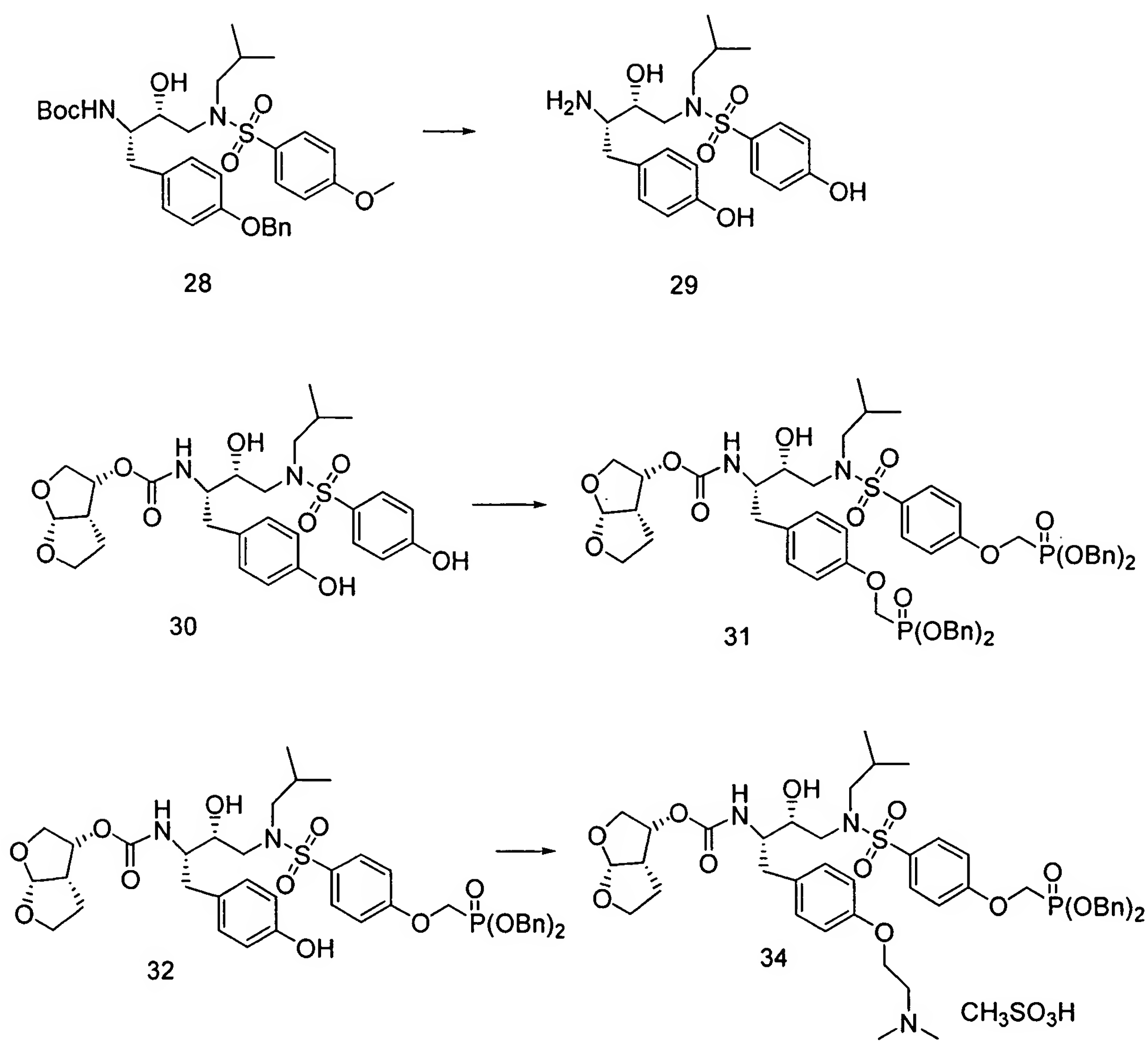


20 21

Scheme D3



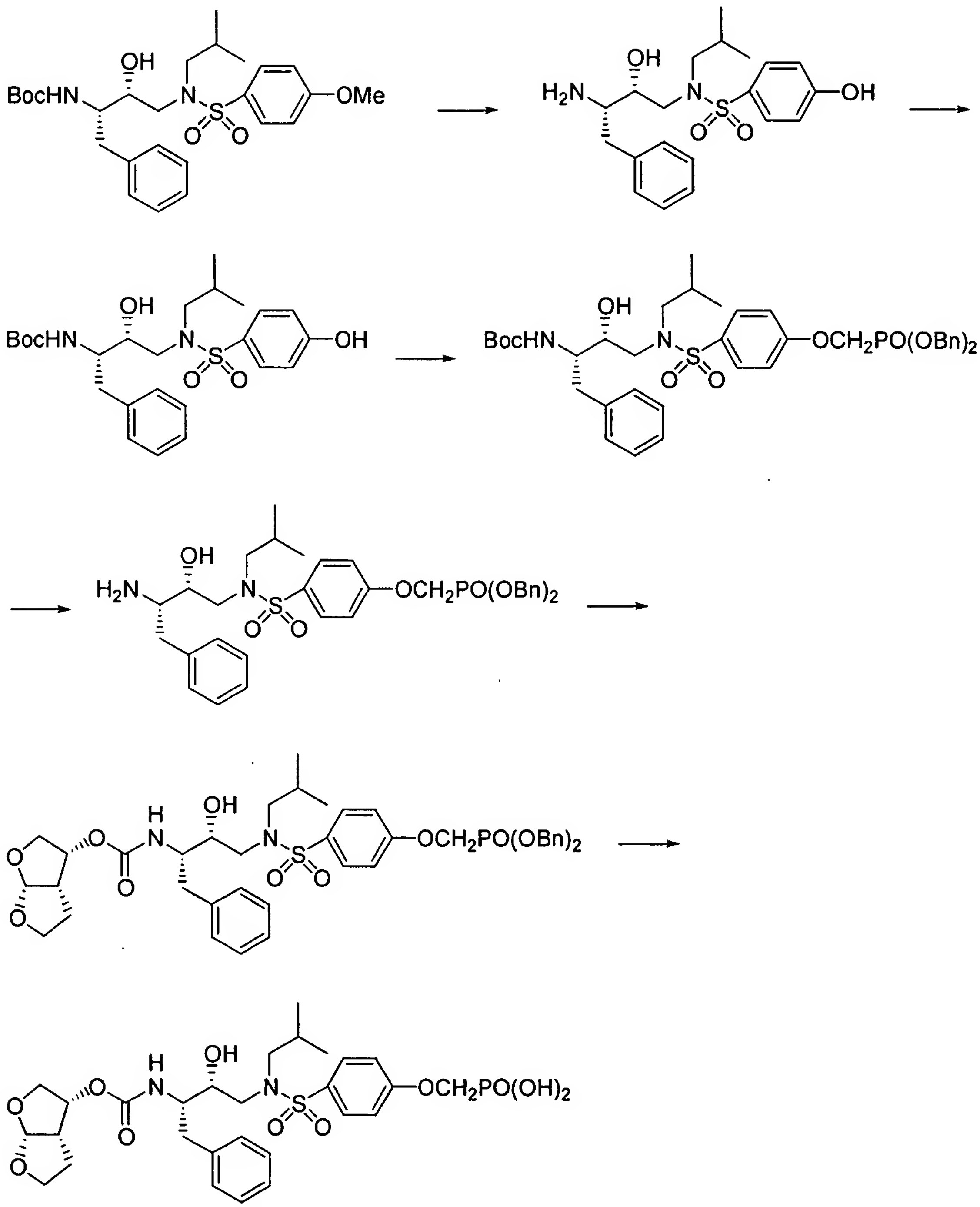
Scheme D4



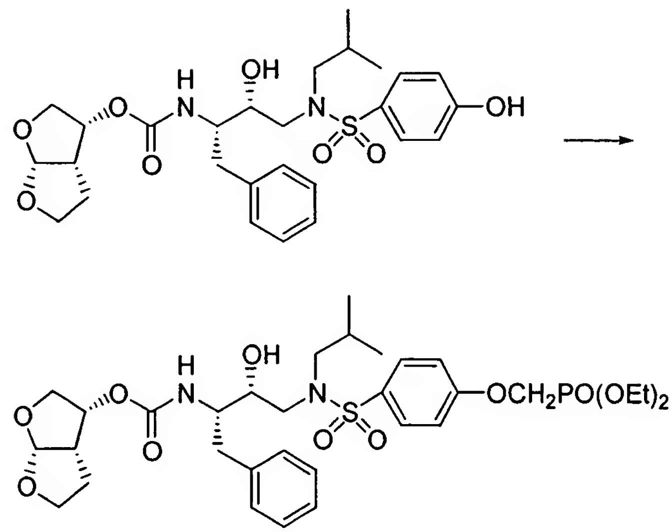
Scheme Section E

Schemes E1-E3 are described in the examples.

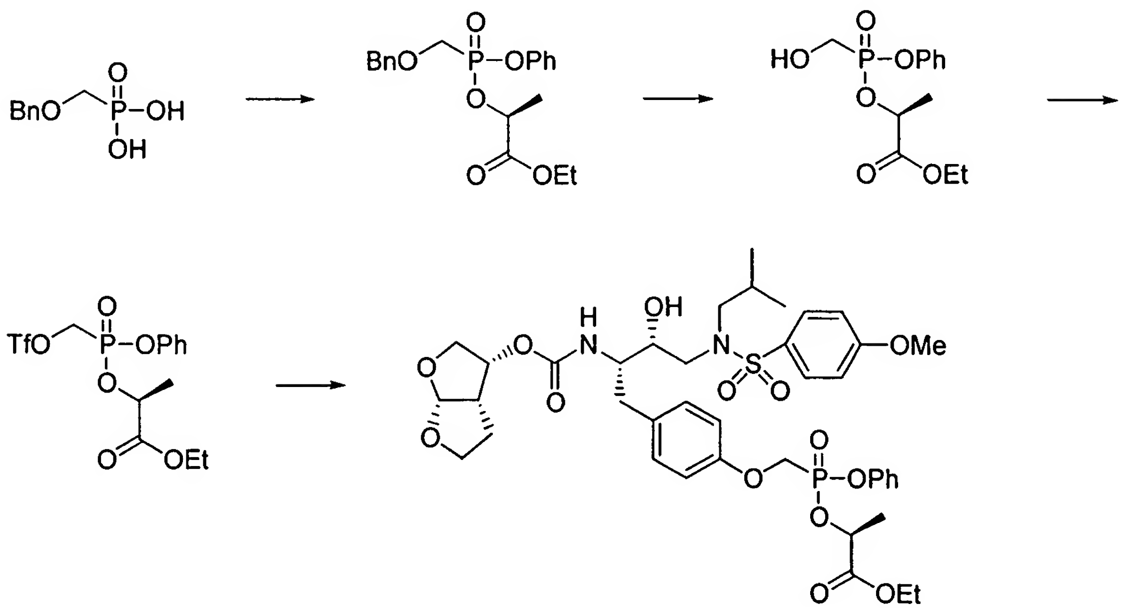
Scheme E1



Scheme E2



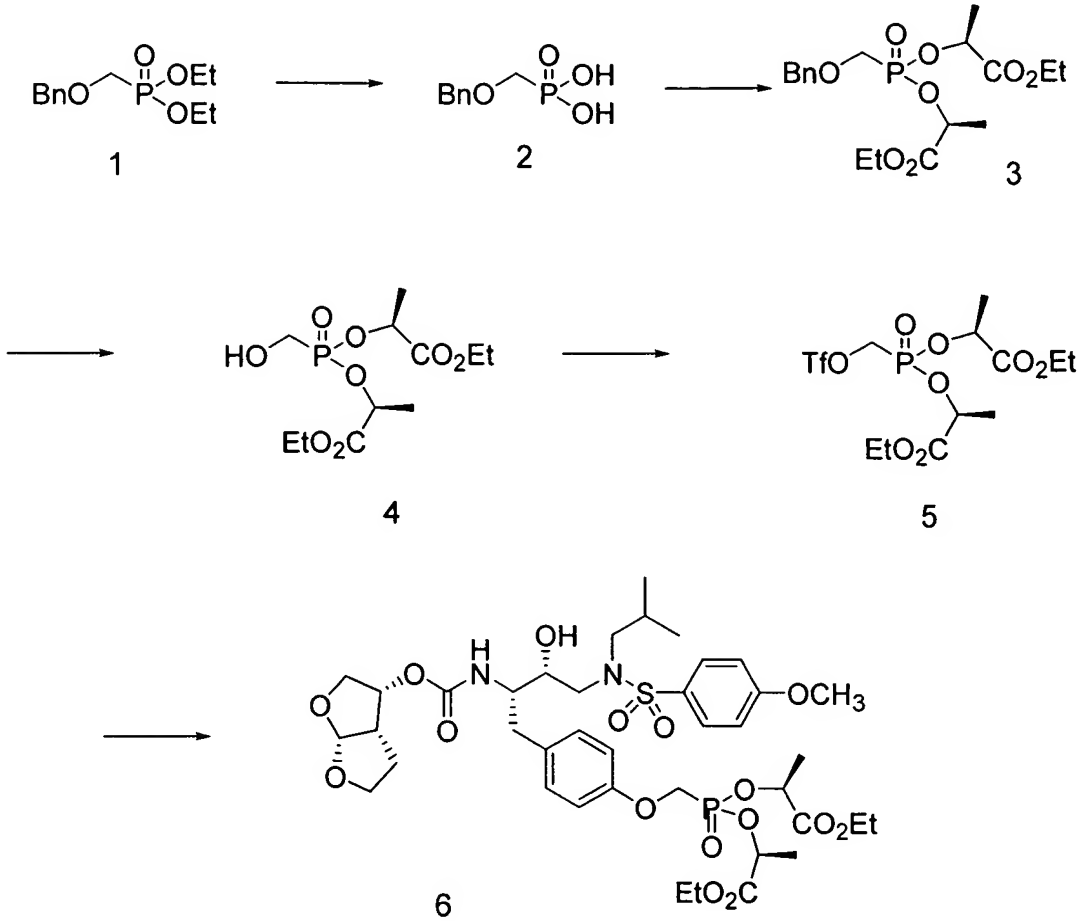
Scheme E3



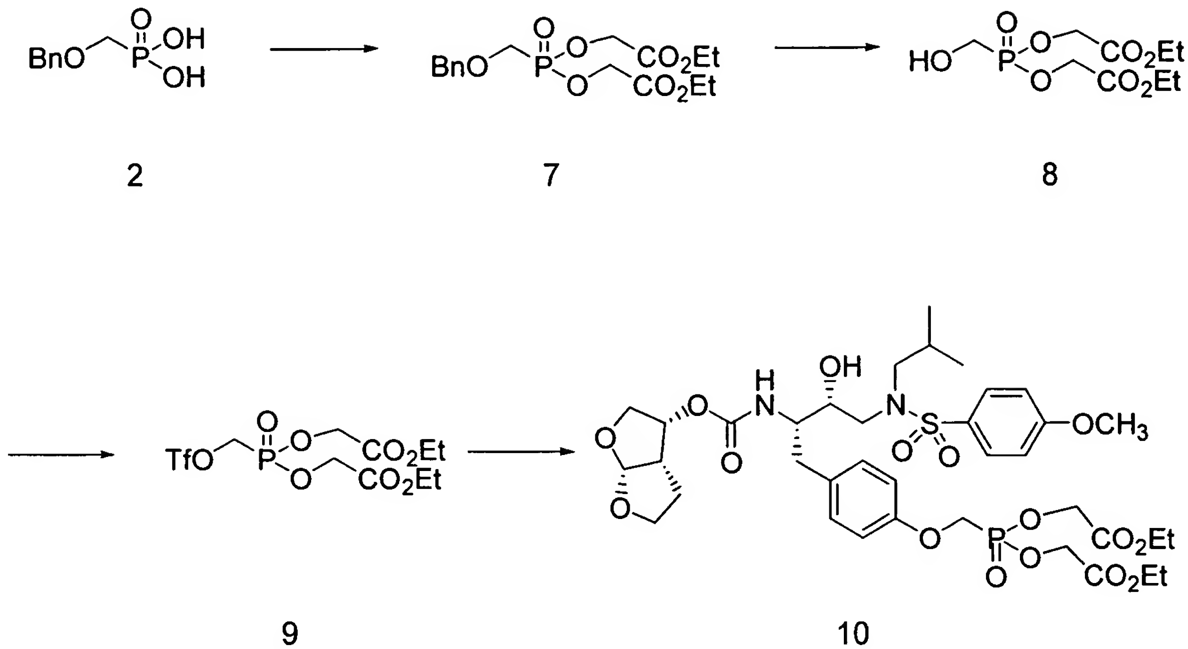
Scheme Section F

Schemes F1-F5 are described in the examples.

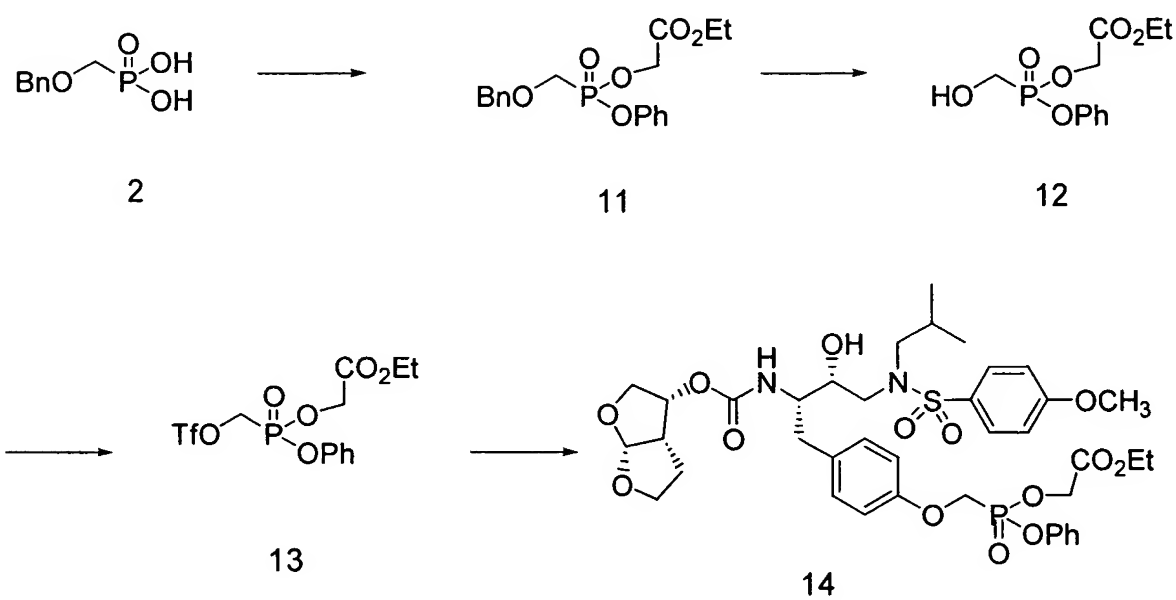
Scheme F1



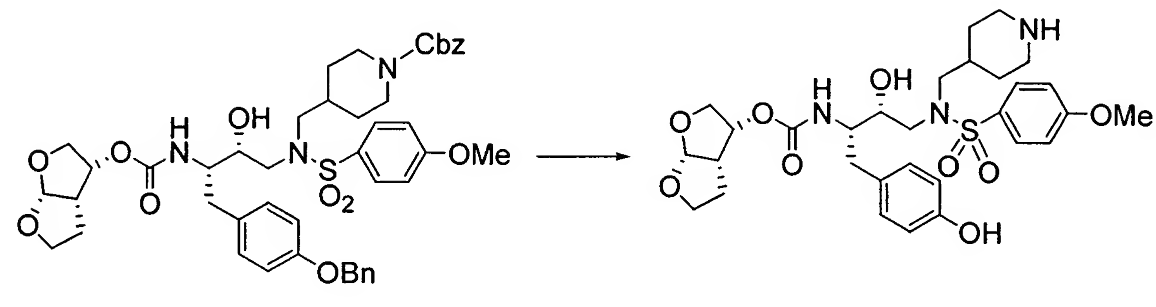
Scheme F2



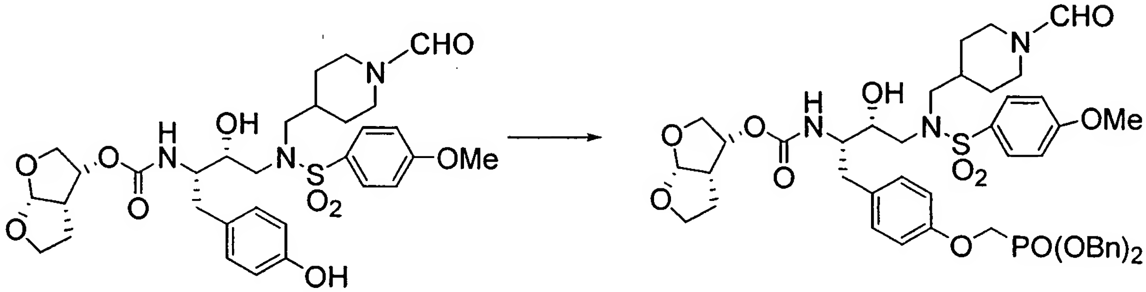
Scheme F3



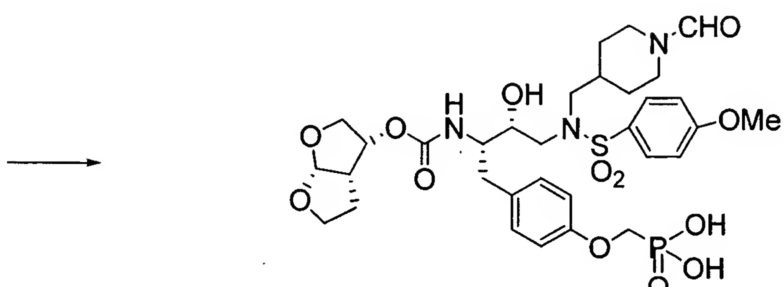
Scheme F4



15 16

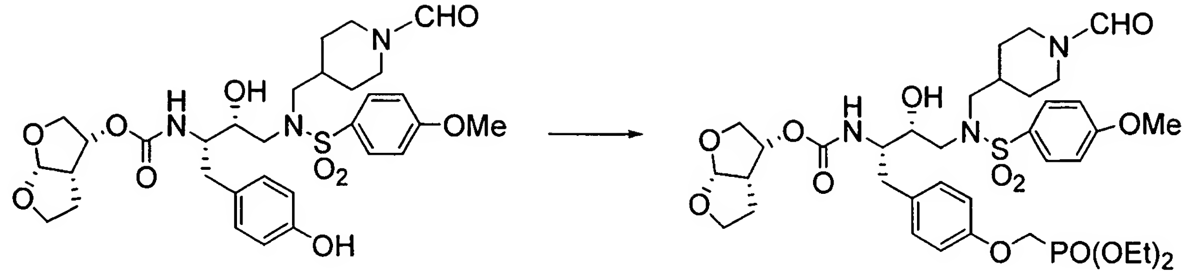


17 18

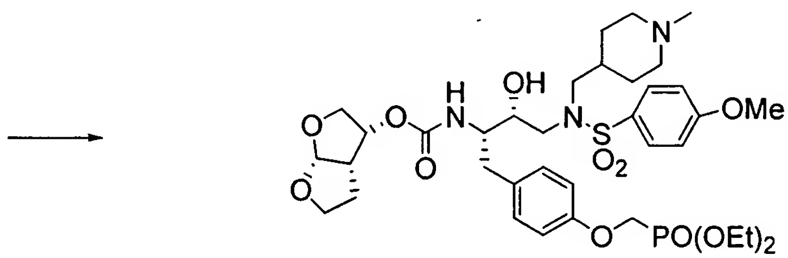


19

Scheme F5



17 20

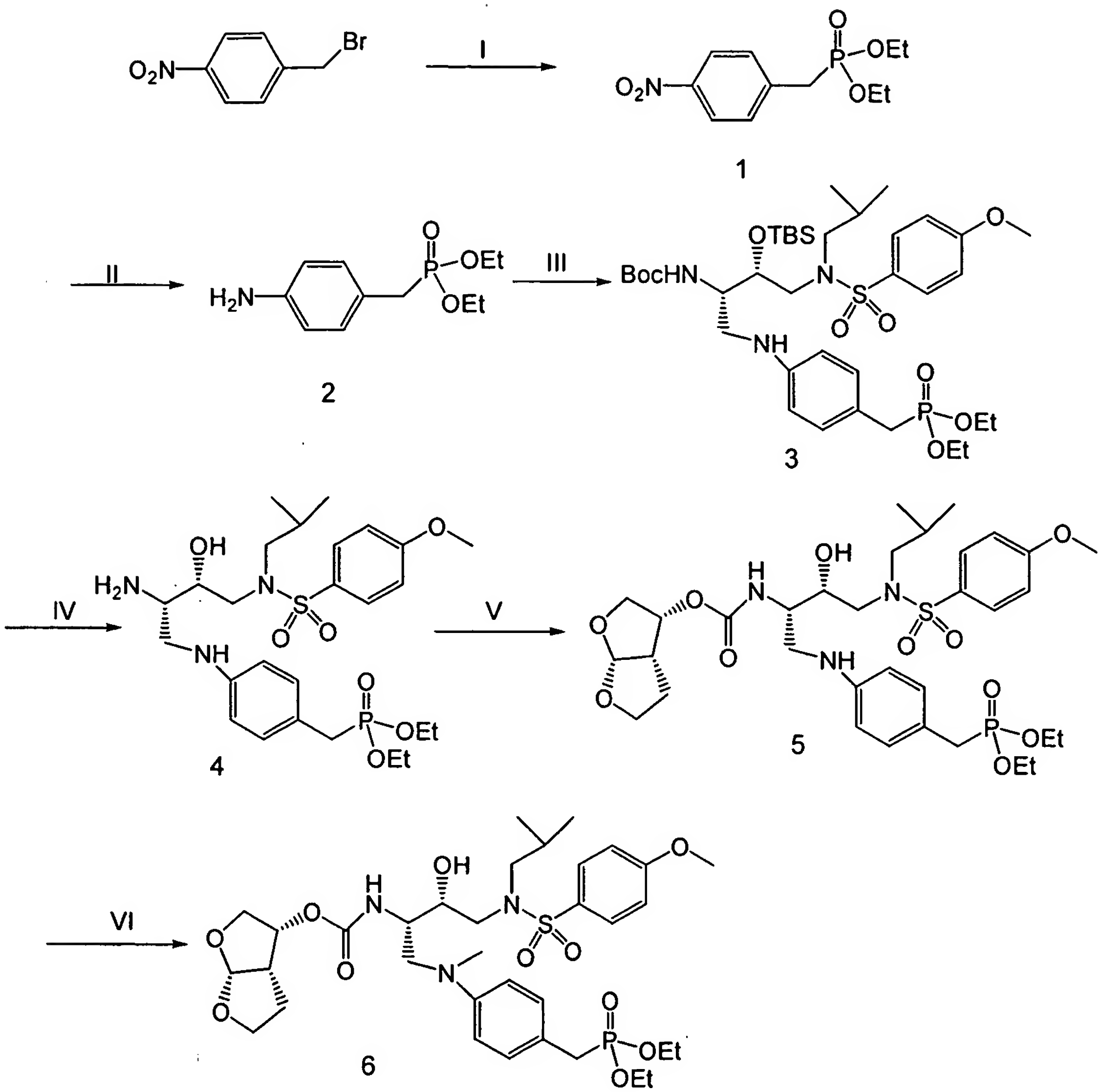


21

Scheme Section G

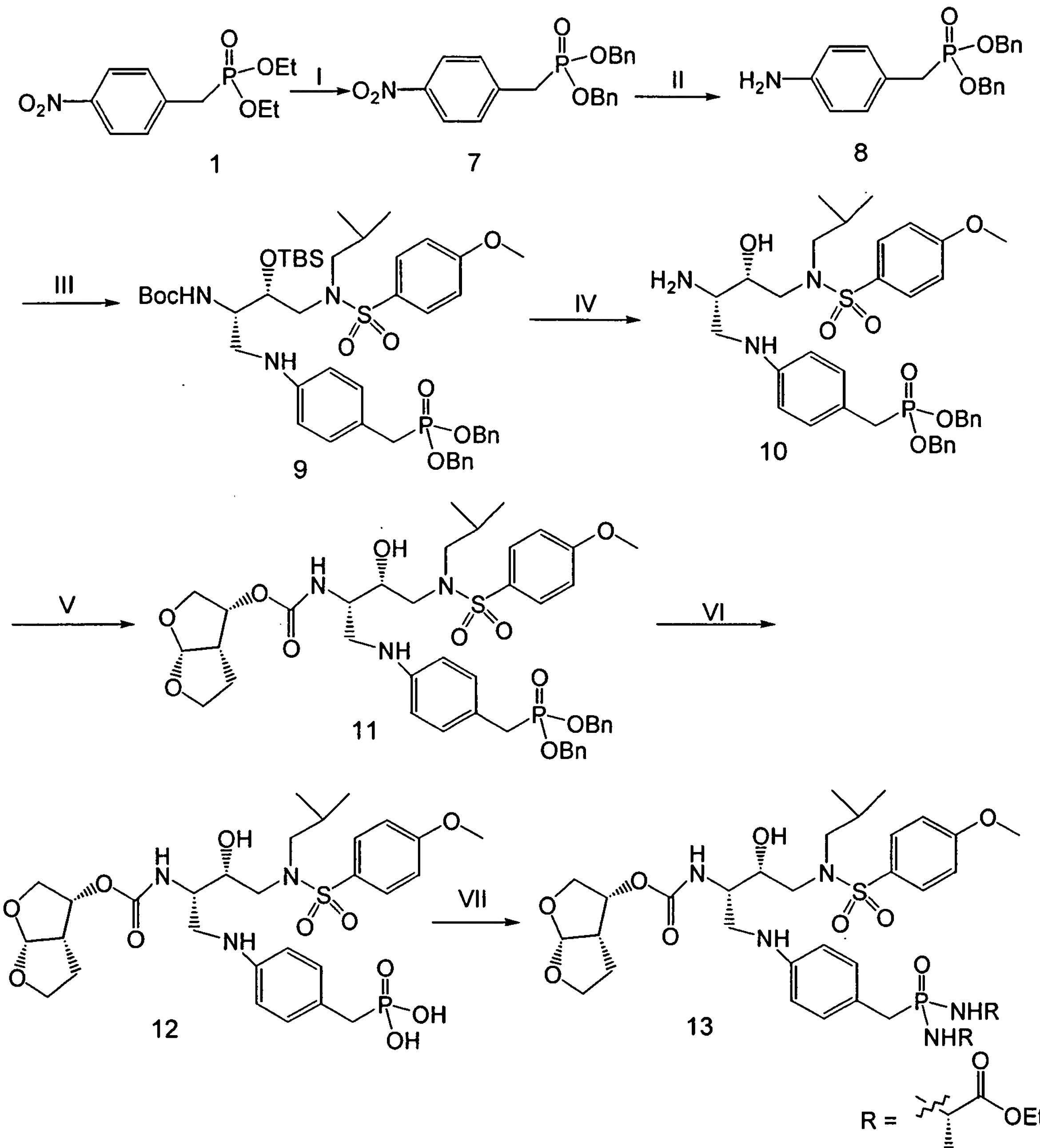
Schemes G1 to G9 are described in the examples.

Scheme G1



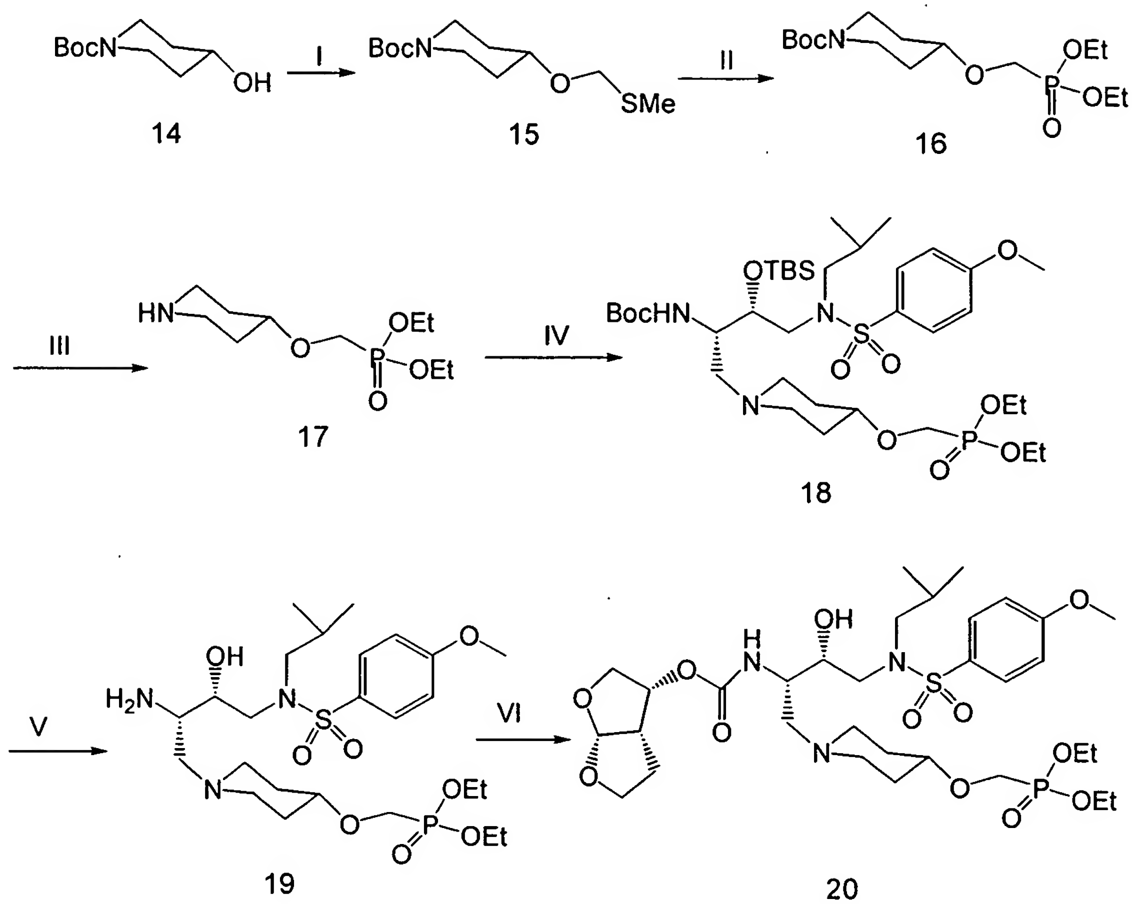
I. $P(OEt)_3$/120 C; II. H_2/10%Pd-C; III. See Scheme Section H, Scheme 13, Compound 48 /$NaBH_3CN$/HOAc/MeOH; IV. a. TFA; b. n-Bu_4NF;V. bisfurancarbonate/DMAP; VI. HCHO/$NaBH_3CN$/HOAc/MeOH

Scheme G2



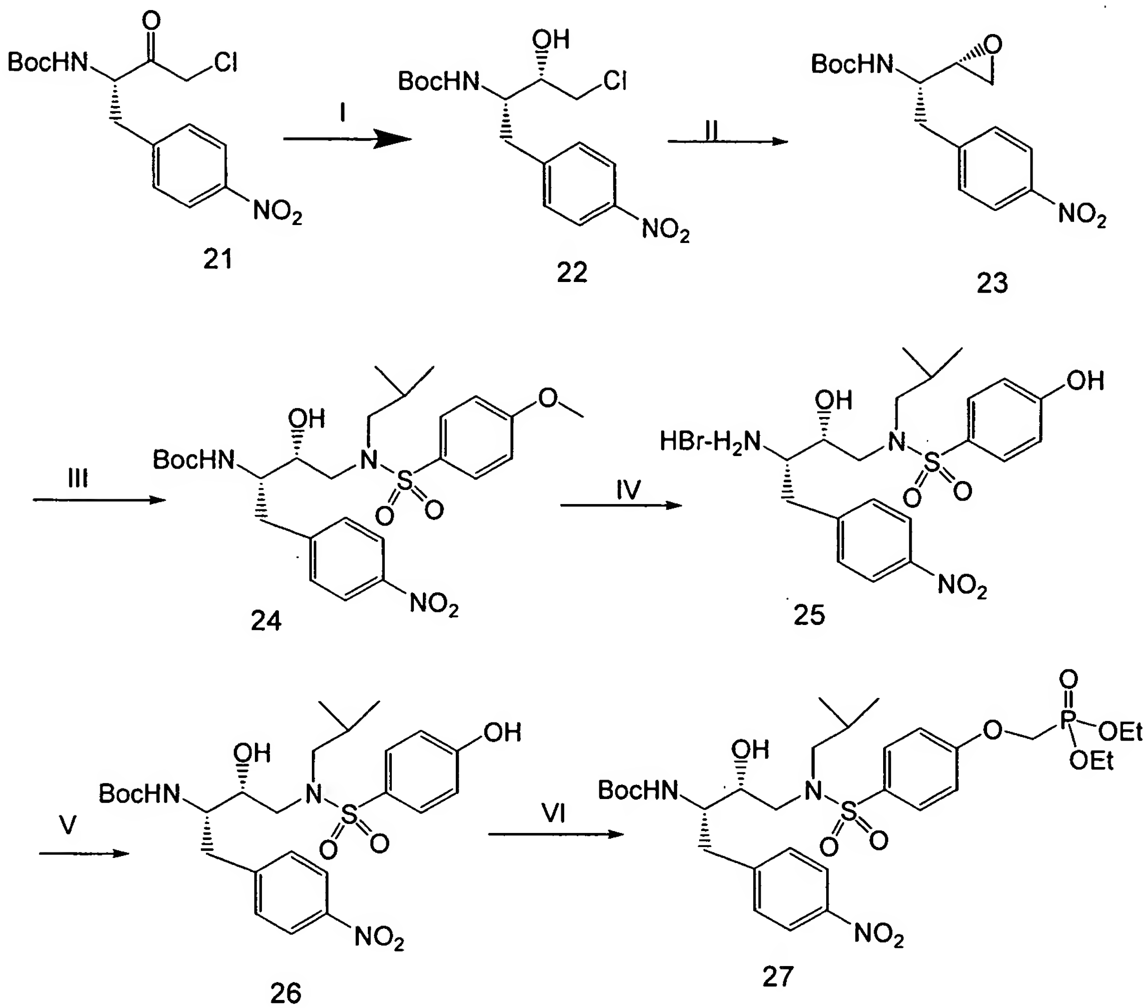
I. a.TMSBr; b. $SOCl_2$/60 C; c. BnOH/Et_3N; II. Zn/HOAc; III. See Scheme Section H, Scheme 13, Compound 48 /$NaBH_3CN$/HOAc/MeOH; IV. a. TFA; b. n-Bu_4NF; V. bisfurancarbonate/DMAP; VI. H_2/10%Pd-C; VIII.RNH_2/PPh_3/aldrithiol

Scheme G3



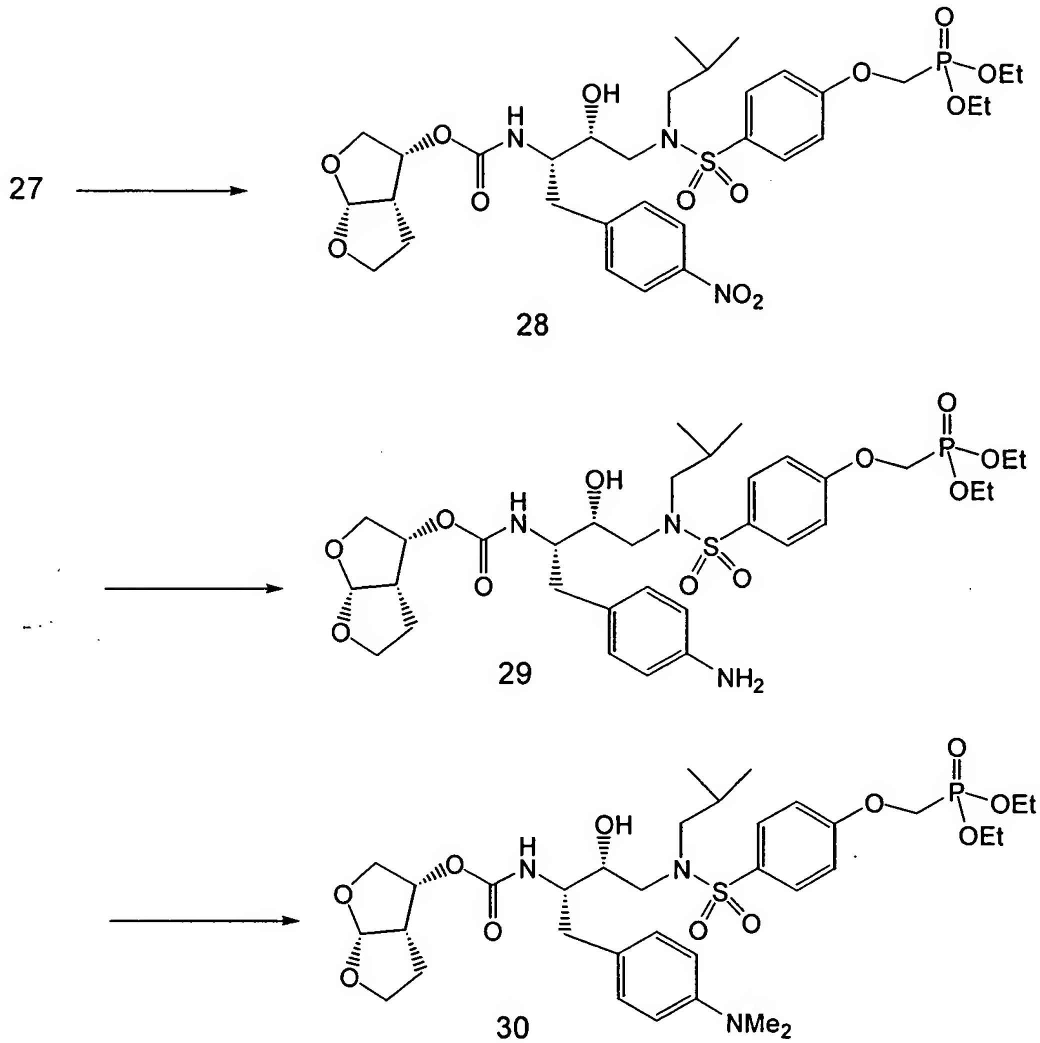
I. a. NaH; b. MTMCl; II. a. $SOCl_2$; b. $P(OEt)_3$/120 C; III. TFA; IV. See Scheme Section H, Scheme 13, Compound 48 /$NaBH_3CN$/HOAc/MeOH; V. a. TFA; b. n-Bu_4NF; VI. bisfurancarbonate/DMAP

Scheme G4



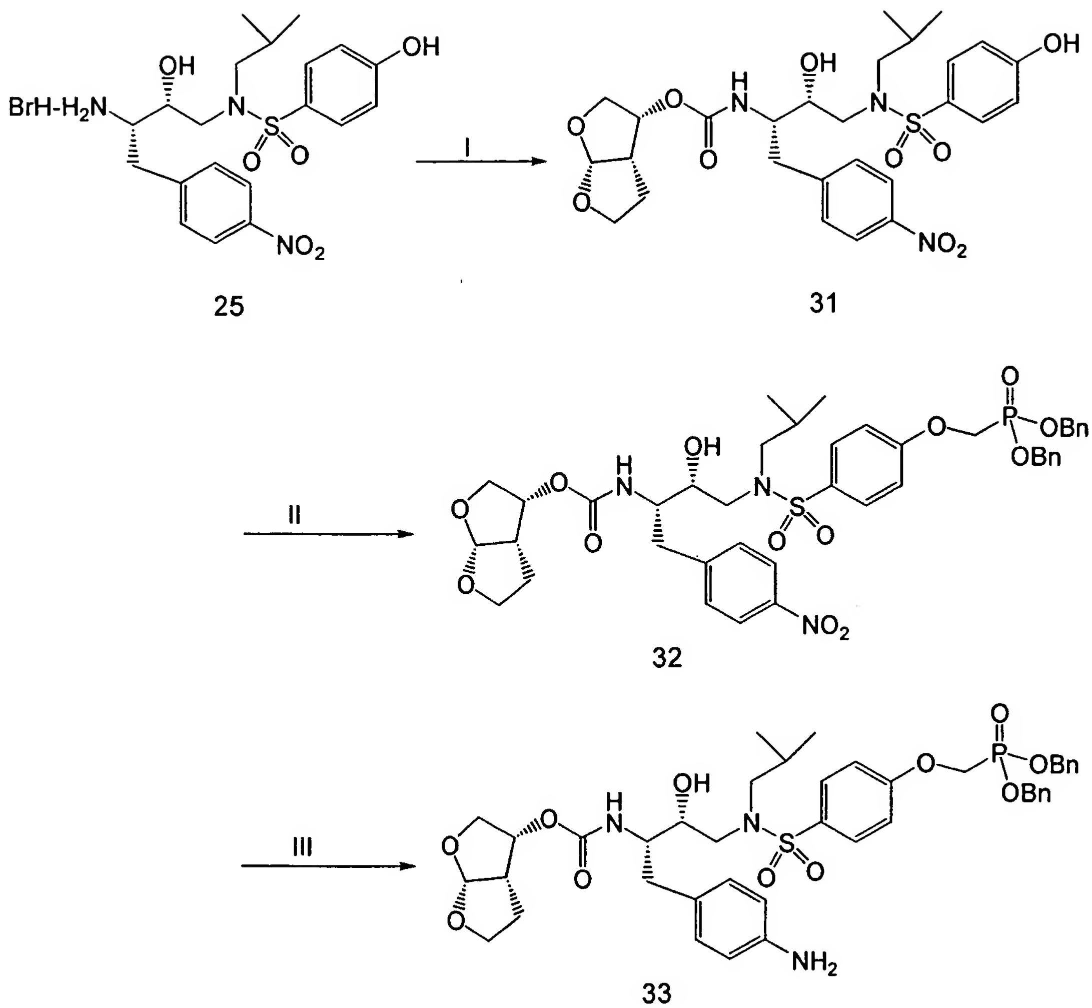
I. $NaBH_4$/THF/H_2O ; II. KOH/EtOH; III. a. isobutylamine/iropropanol/80 C; b. 4-methoxybenzenesulfonyl chloride/Et_3N; IV.BBr_3/CH_2Cl_2; V. Boc_2O/$NaHCO_3$; VI. $TfOCH_2PO(OEt)_2$/Cs_2CO_3

Scheme G5



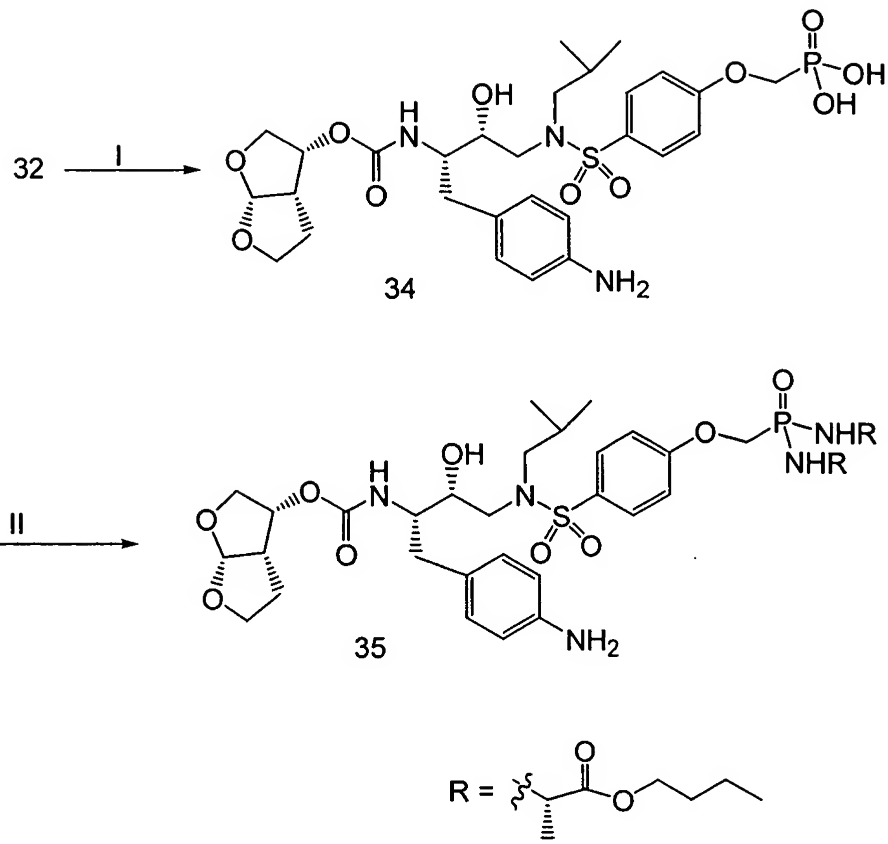
I. TFA/CH_2Cl_2; b. bisfurancarbonate/DMAP ; II. H_2/10% Pd-C/EtOH;
III. $HCHO/NaBH_3CN/HOAc/MeOH$

Scheme G6



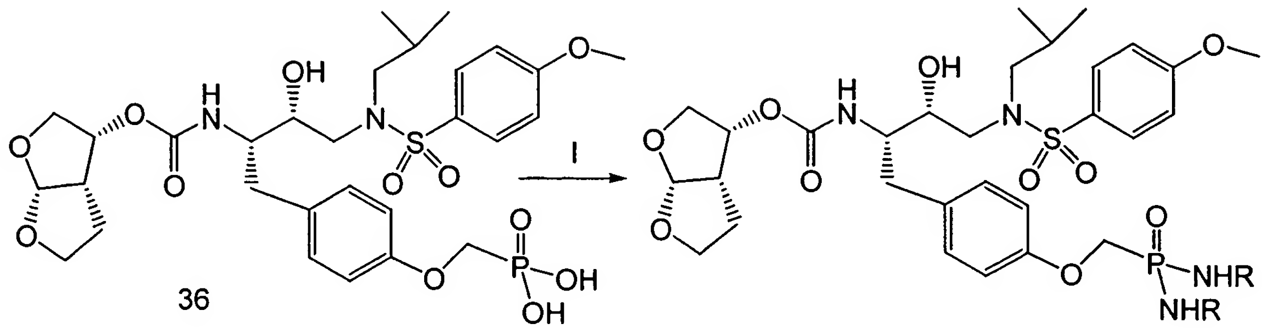
I.a. TMSCl/Et_3N; b. bisfurancarbonate/DMAP; c. n-Bu_4NF/HOAc; II. $TfOCH_2PO(OBn)_2/Cs_2CO_3$; III. Zn/HOAc

Scheme G7



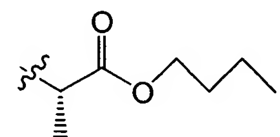
I. H_2/10% Pd-C; II. RNH_2/PPh_3/Aldrithiol/diisopropylethylamine/pyridine

Scheme G8

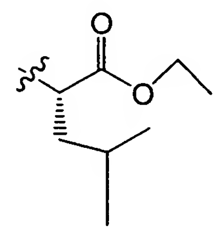


I. RNH_2/PPh_3/Aldrithiol/diisopropylethylamine/pyridine

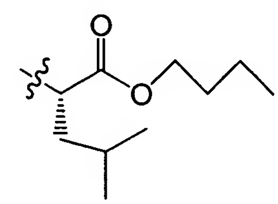
37 R =



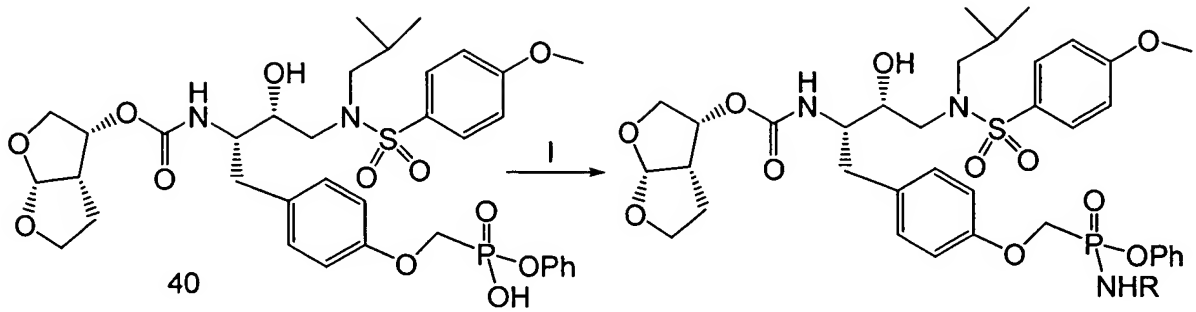
38 R =



39 R =

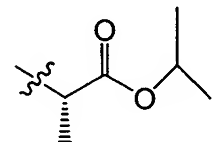


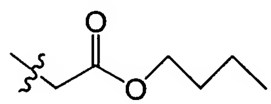
Scheme G9



40

I. RNH_2/PPh_3/Aldrithiol/diisopropylethylamine/pyridine

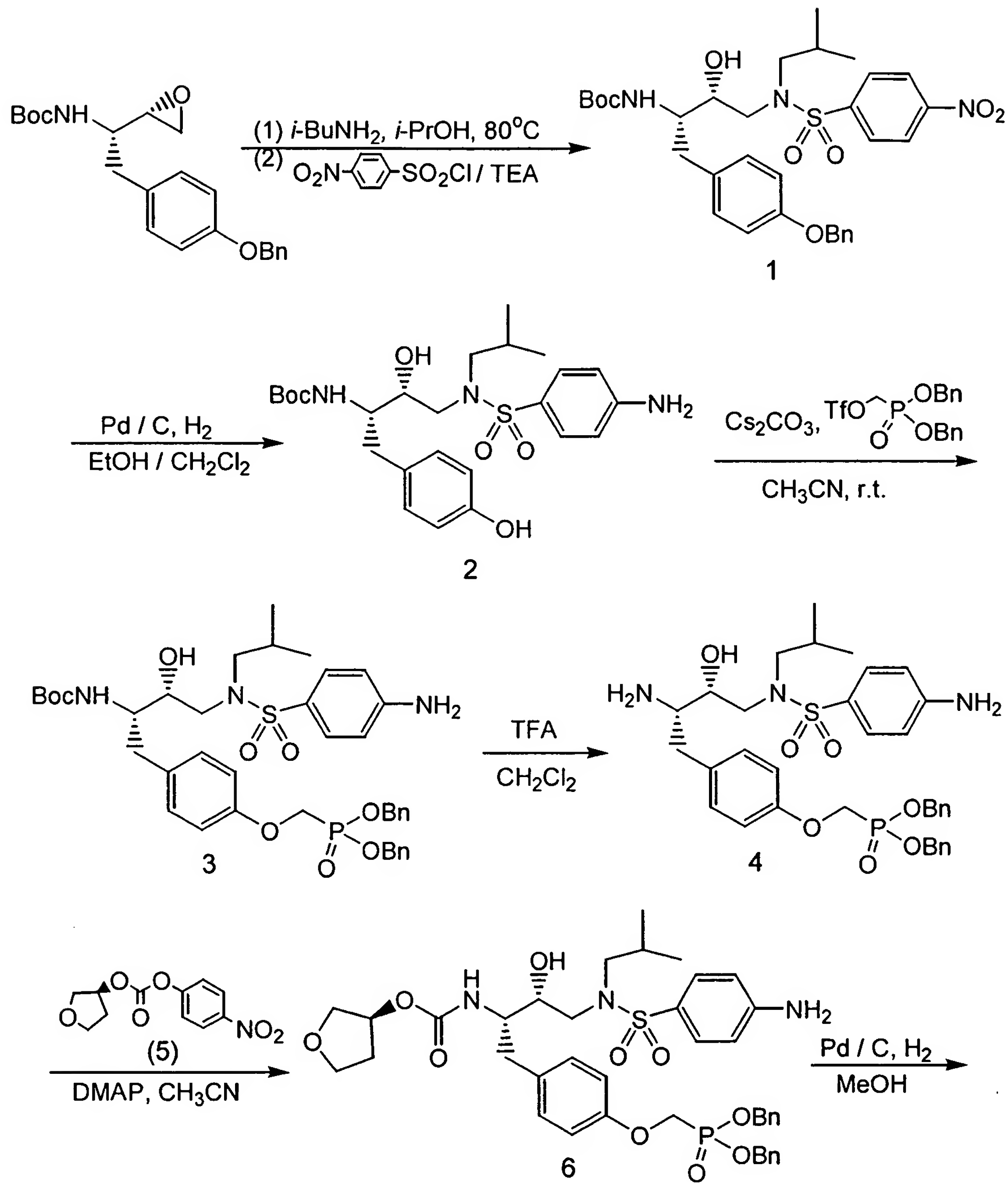
41 R = 

42 R = 

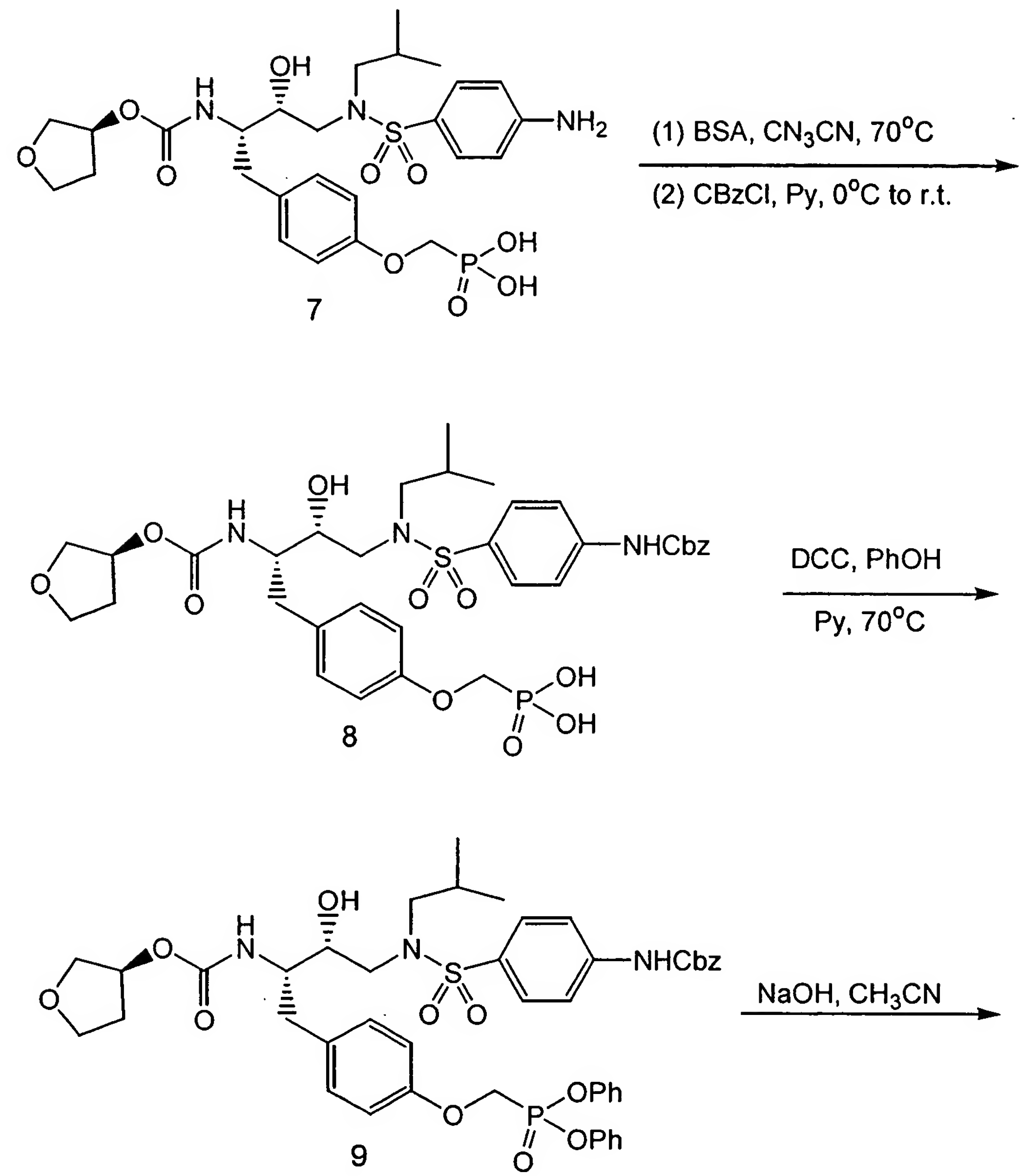
Scheme Section H

Schemes H1-H14 are described in the examples.

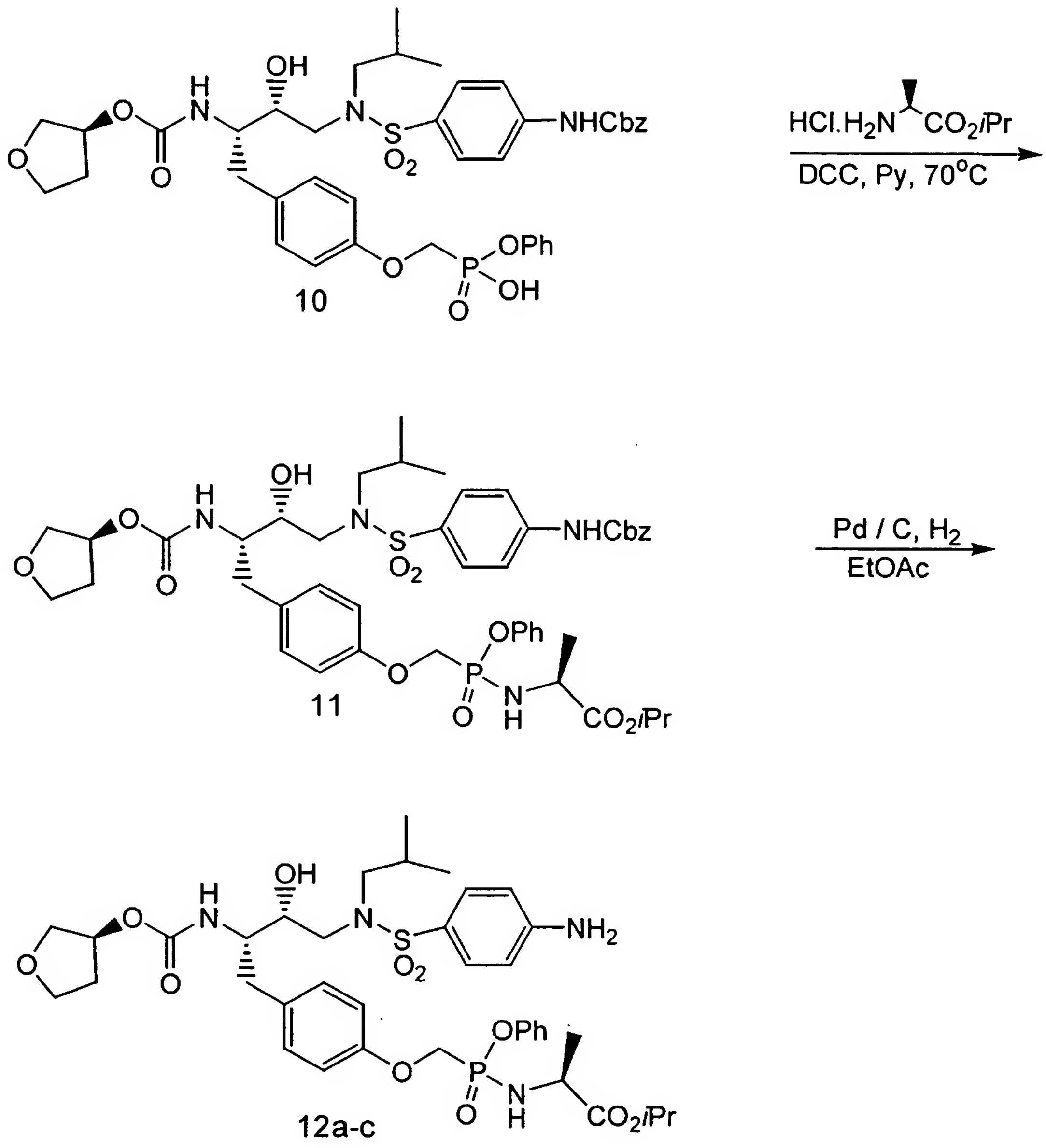
Scheme H1



Scheme H2

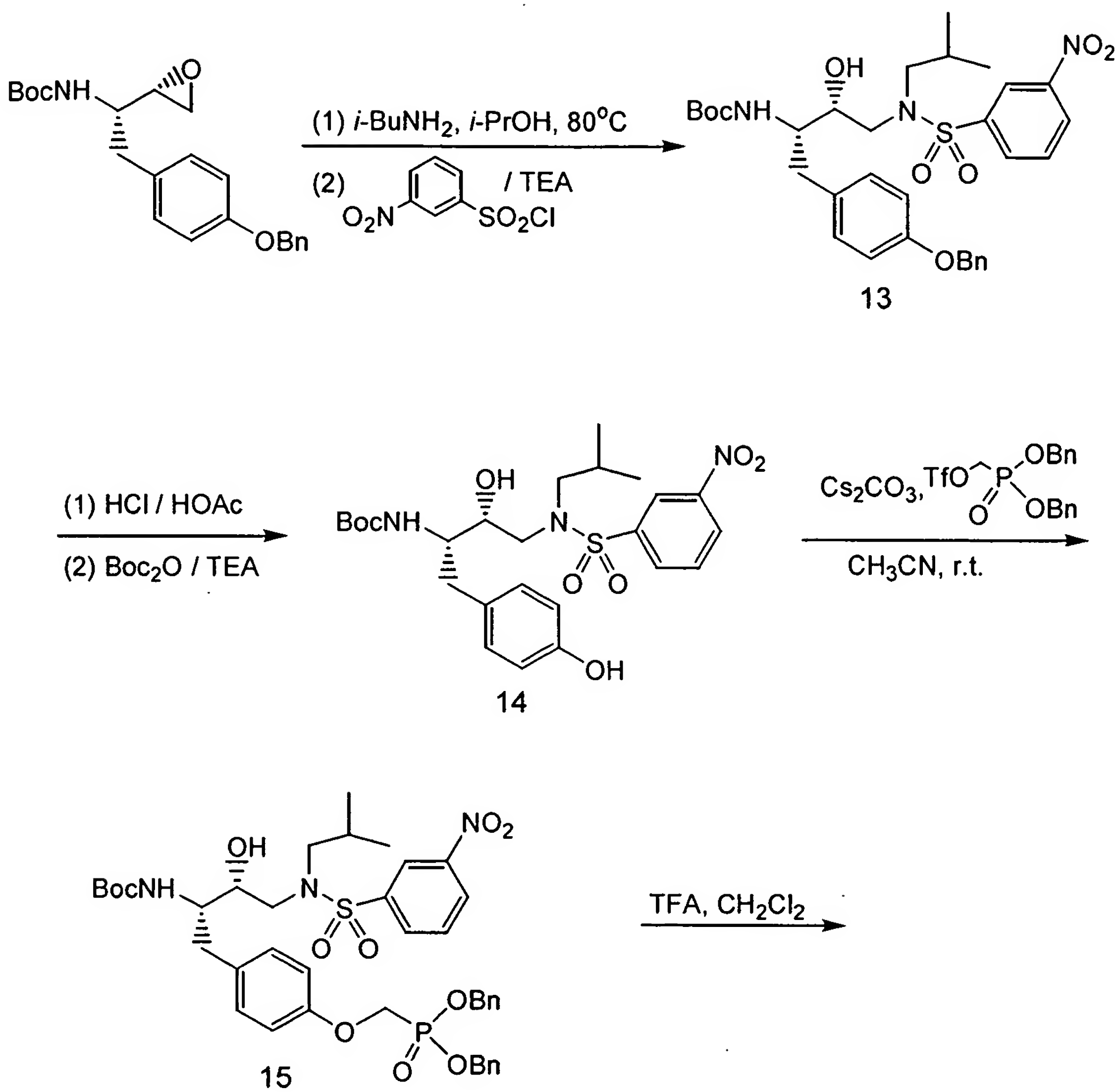

OH
H
N
O
O
N
S
O
O
NH2
(1) BSA, CN3CN, 70°C
(2) CBzCl, Py, 0°C to r.t.
O
P
OH
OH
O
7
NHCbz
DCC, PhOH
Py, 70°C
8
OPh
OPh
NaOH, CH3CN
9

Scheme H3

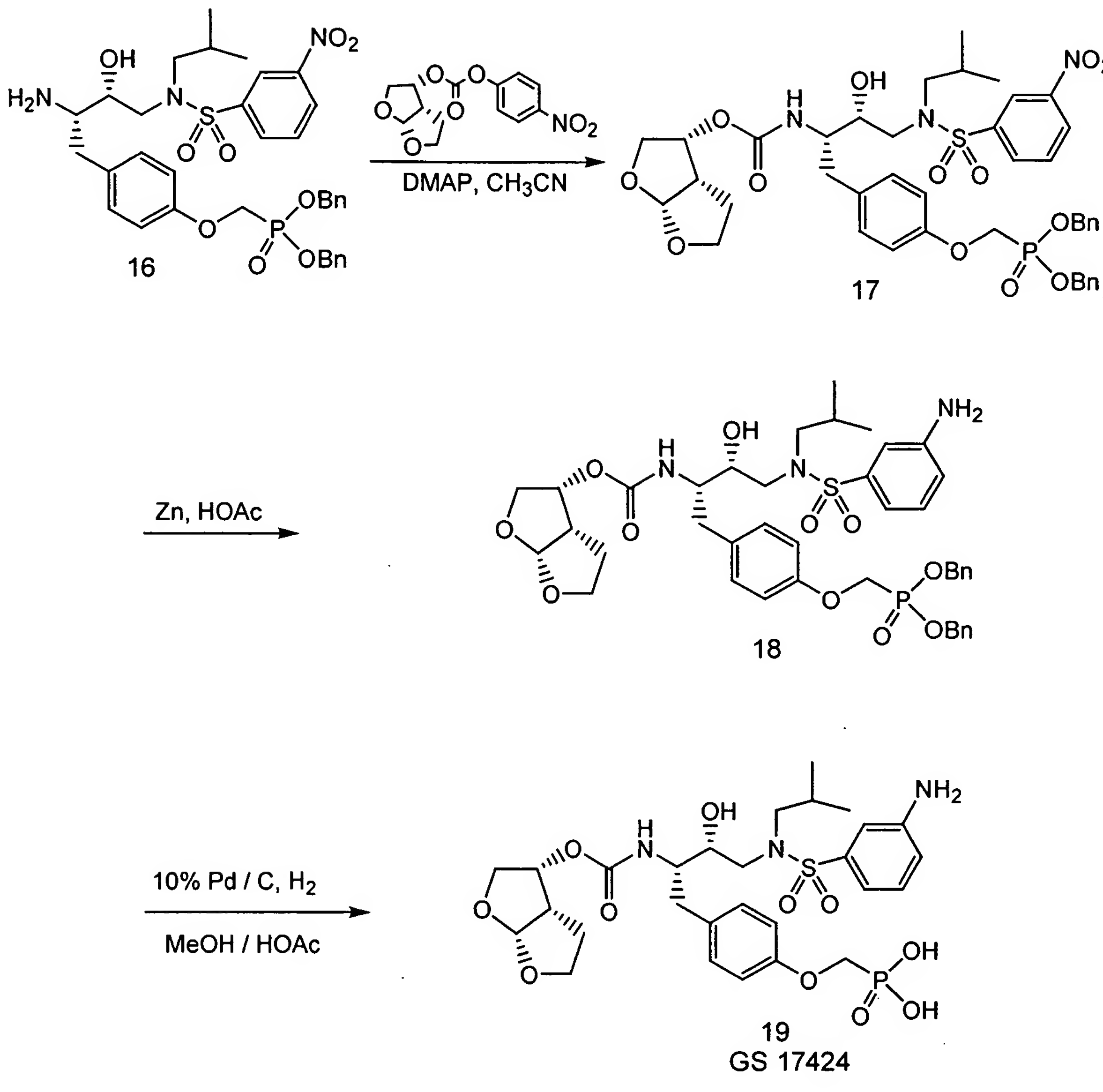


12a, GS 108577 (isomer A / B = 1 : 1)
12b, GS 108578 (isomer A)
12c, GS 108579 (isomer B)

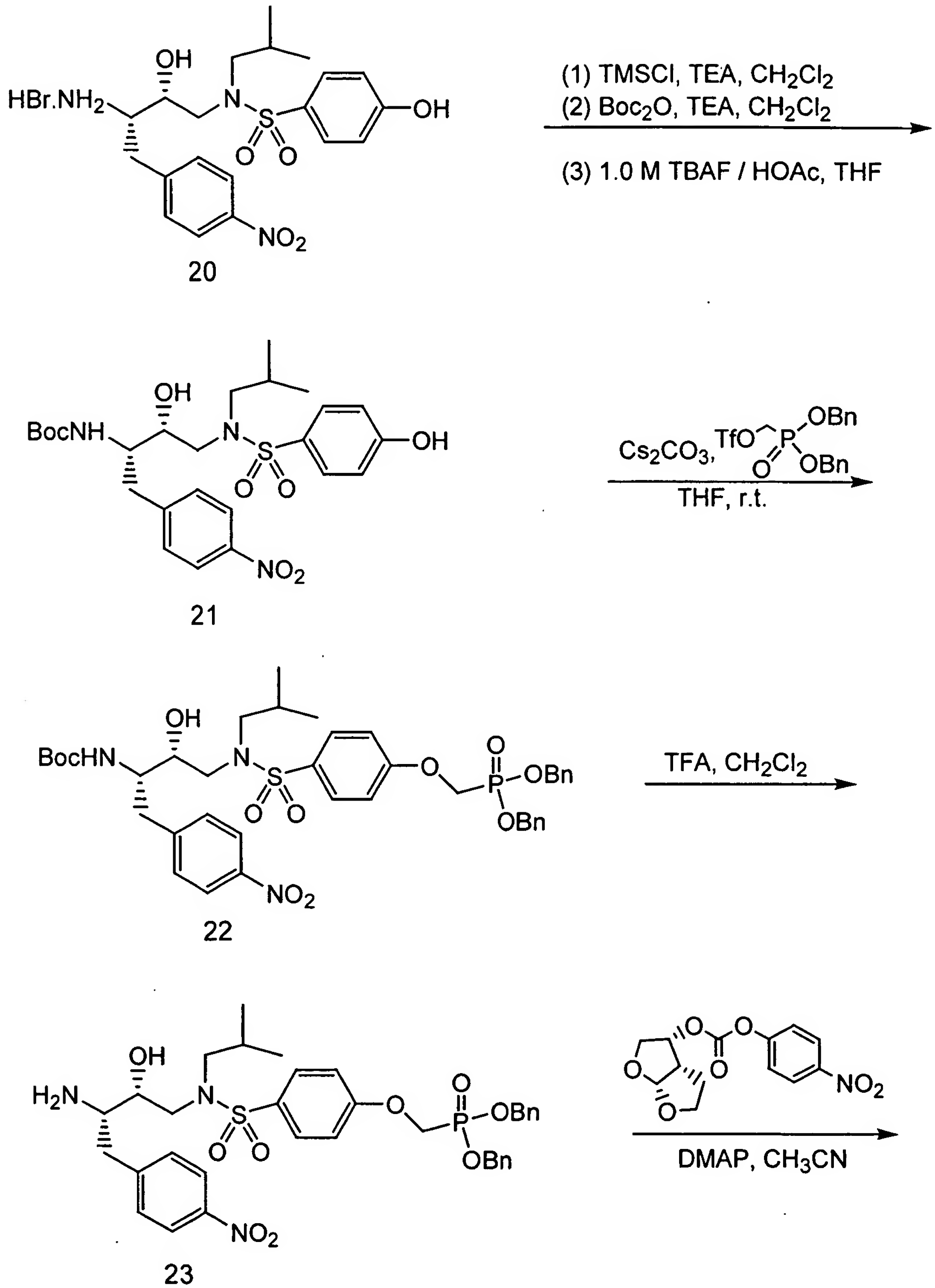
Scheme H4


BocNH
OBn
(1) i-BuNH2, i-PrOH, 80°C
(2) / TEA
O2N
SO2Cl
OH
NO2
N
S
O
13
(1) HCl / HOAc
(2) Boc2O / TEA
14
Cs2CO3, TfO
P
OBn
CH3CN, r.t.
15
TFA, CH2Cl2

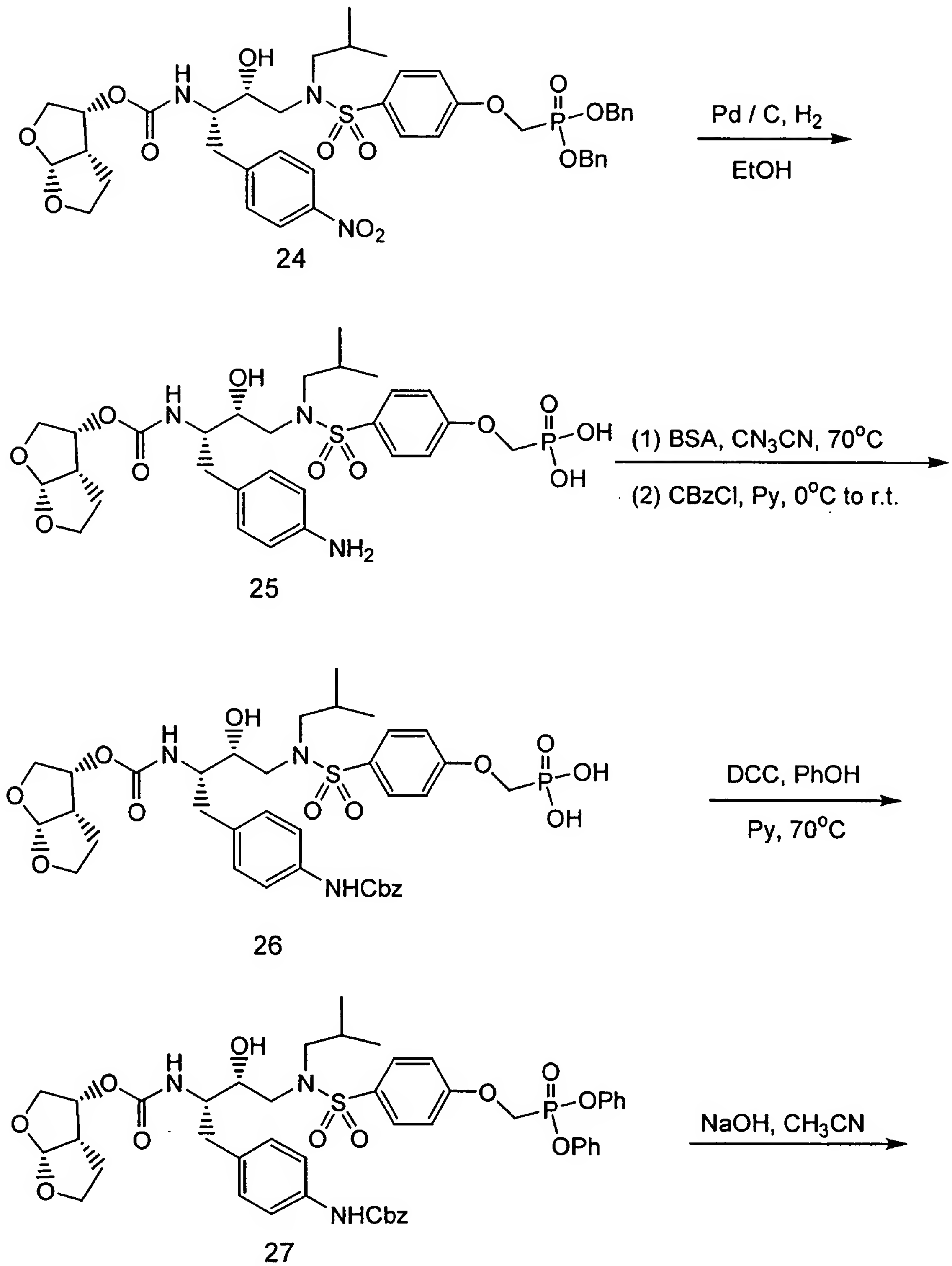
Scheme H5



Scheme H6

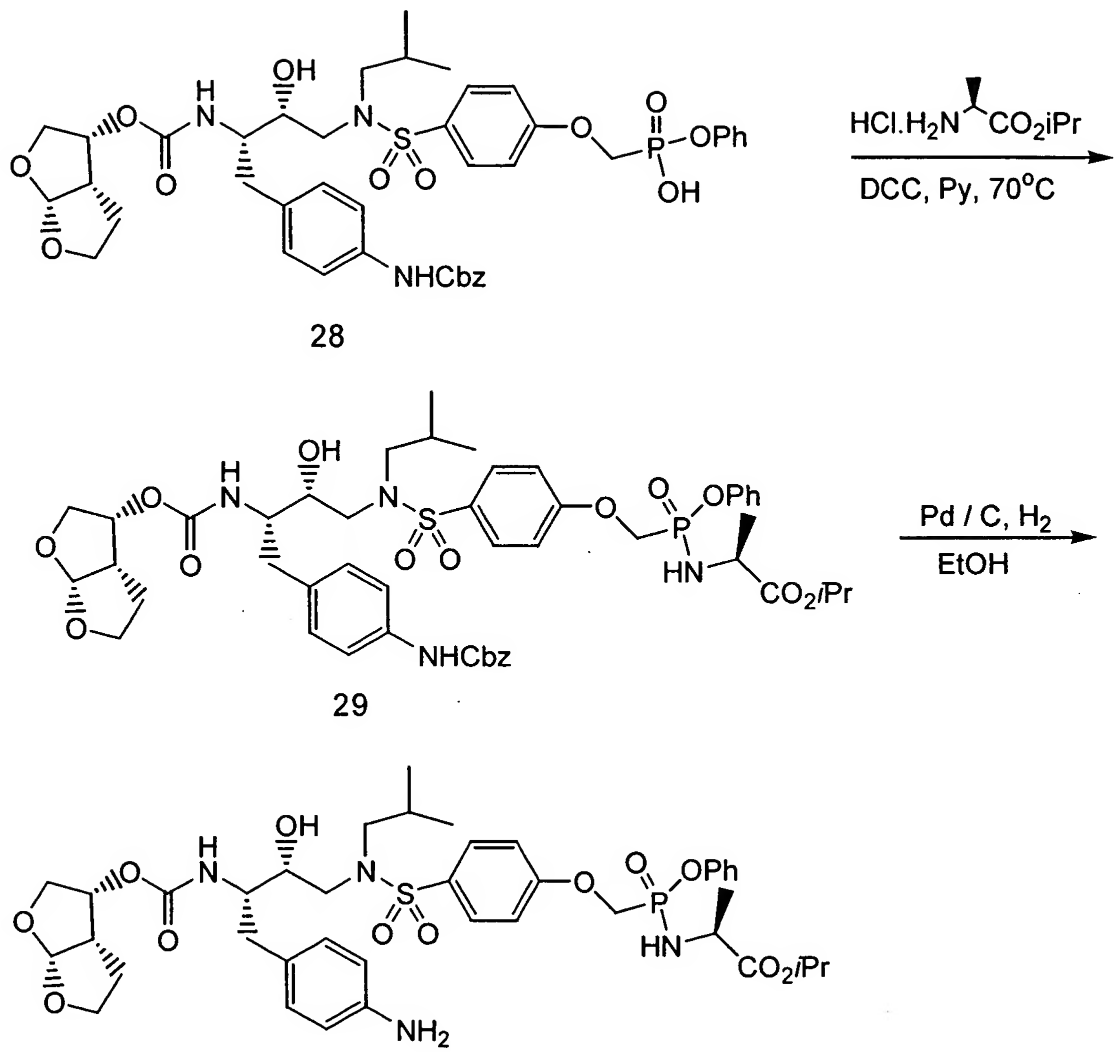

HBr.NH2
OH
OH
NO2
20
(1) TMSCl, TEA, CH2Cl2
(2) Boc2O, TEA, CH2Cl2
(3) 1.0 M TBAF / HOAc, THF
BocNH
OH
OH
NO2
21
Cs2CO3, TfO P OBn OBn
THF, r.t.
BocHN
OH
O
OBn
OBn
NO2
22
TFA, CH2Cl2
H2N
OH
O
OBn
OBn
NO2
23
NO2
DMAP, CH3CN

Scheme H7



24
Pd / C, H_2
EtOH
25
(1) BSA, CN_3CN, 70°C
(2) CBzCl, Py, 0°C to r.t.
26
DCC, PhOH
Py, 70°C
27
NaOH, CH_3CN

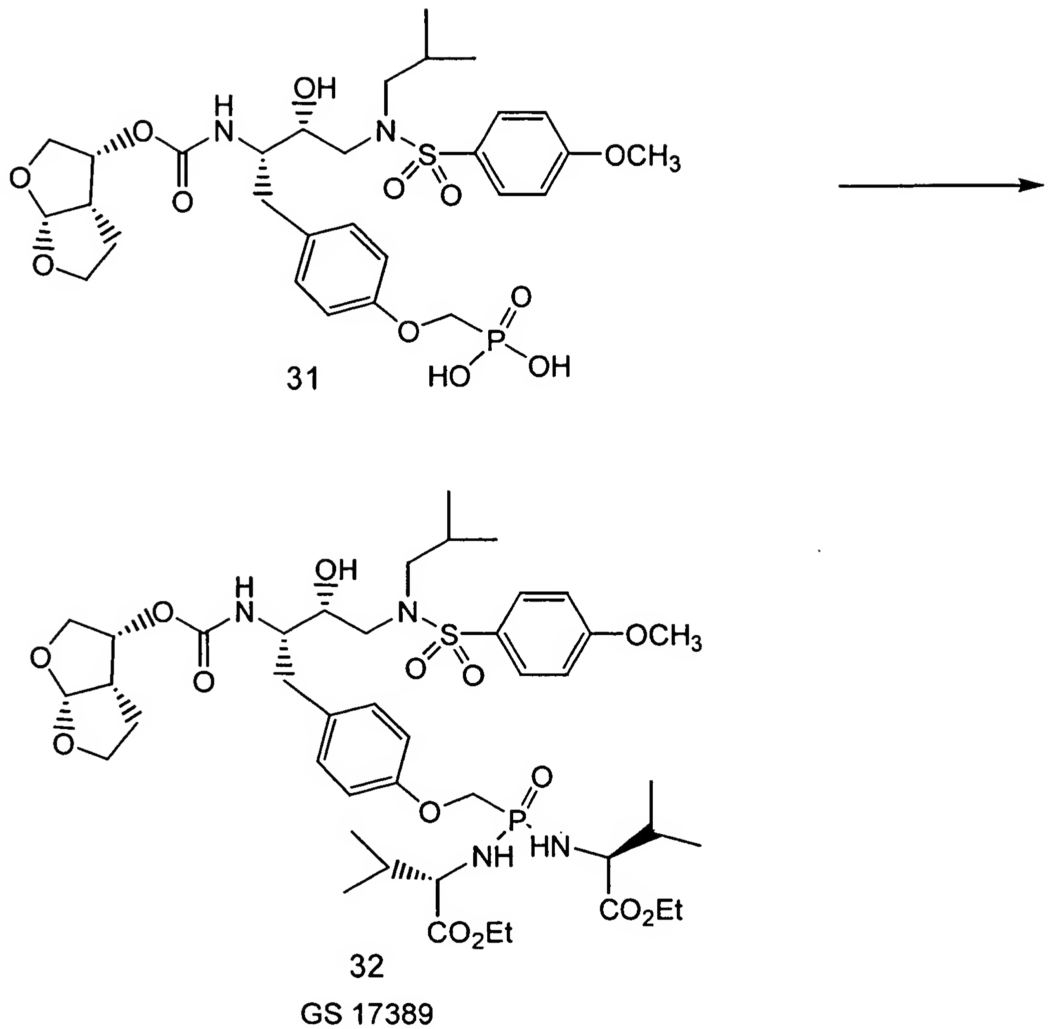
Scheme H8



30 a-b

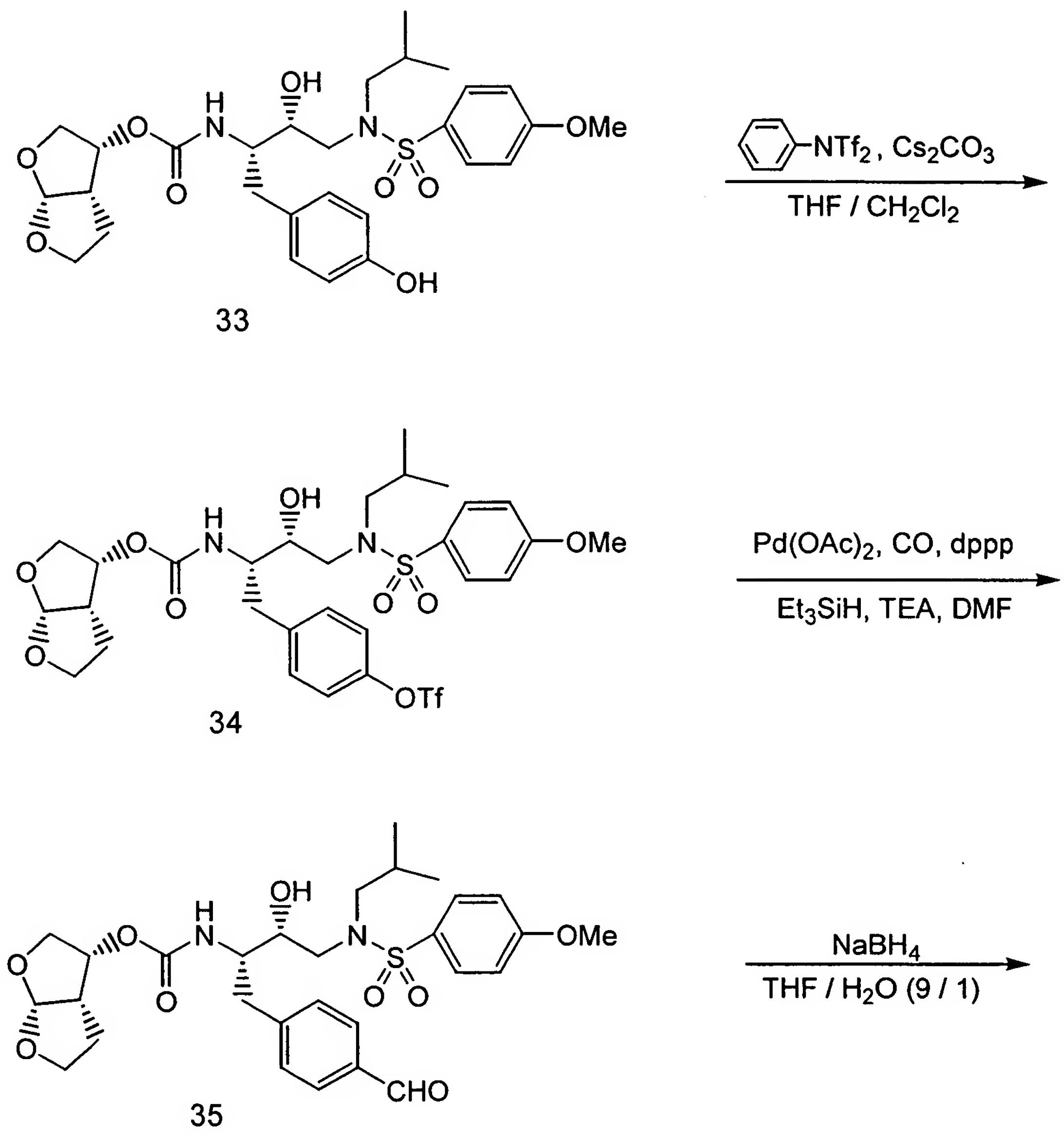
30a R = H, GS 77369
30b R = Et, GS 77425

Scheme H9



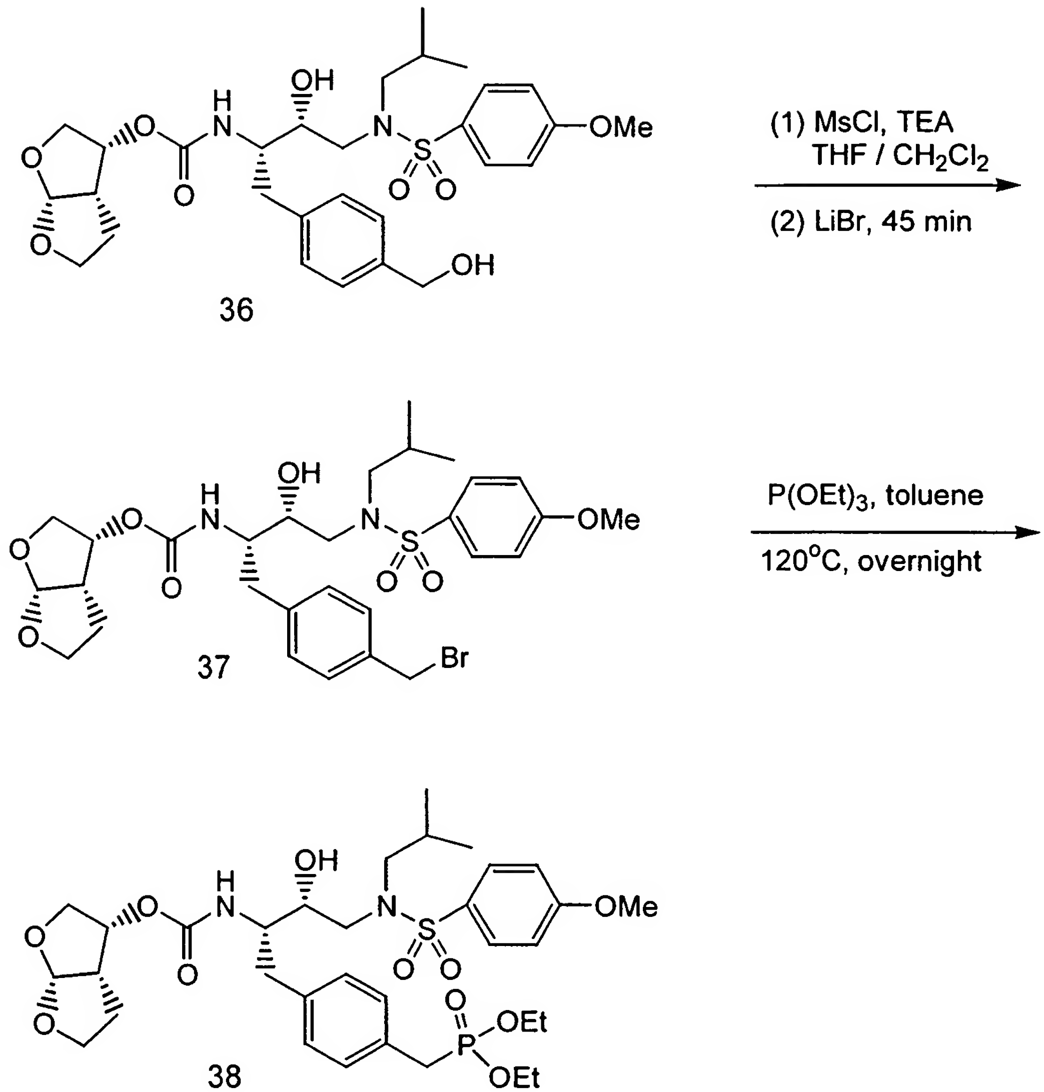
OH
H
N
O
O
O
O
N
S
O
O
OCH3
O
O
P
HO
OH
31
OH
H
N
O
O
O
O
N
S
O
O
OCH3
O
O
P
NH
HN
CO2Et
CO2Et
32
GS 17389

Scheme H10



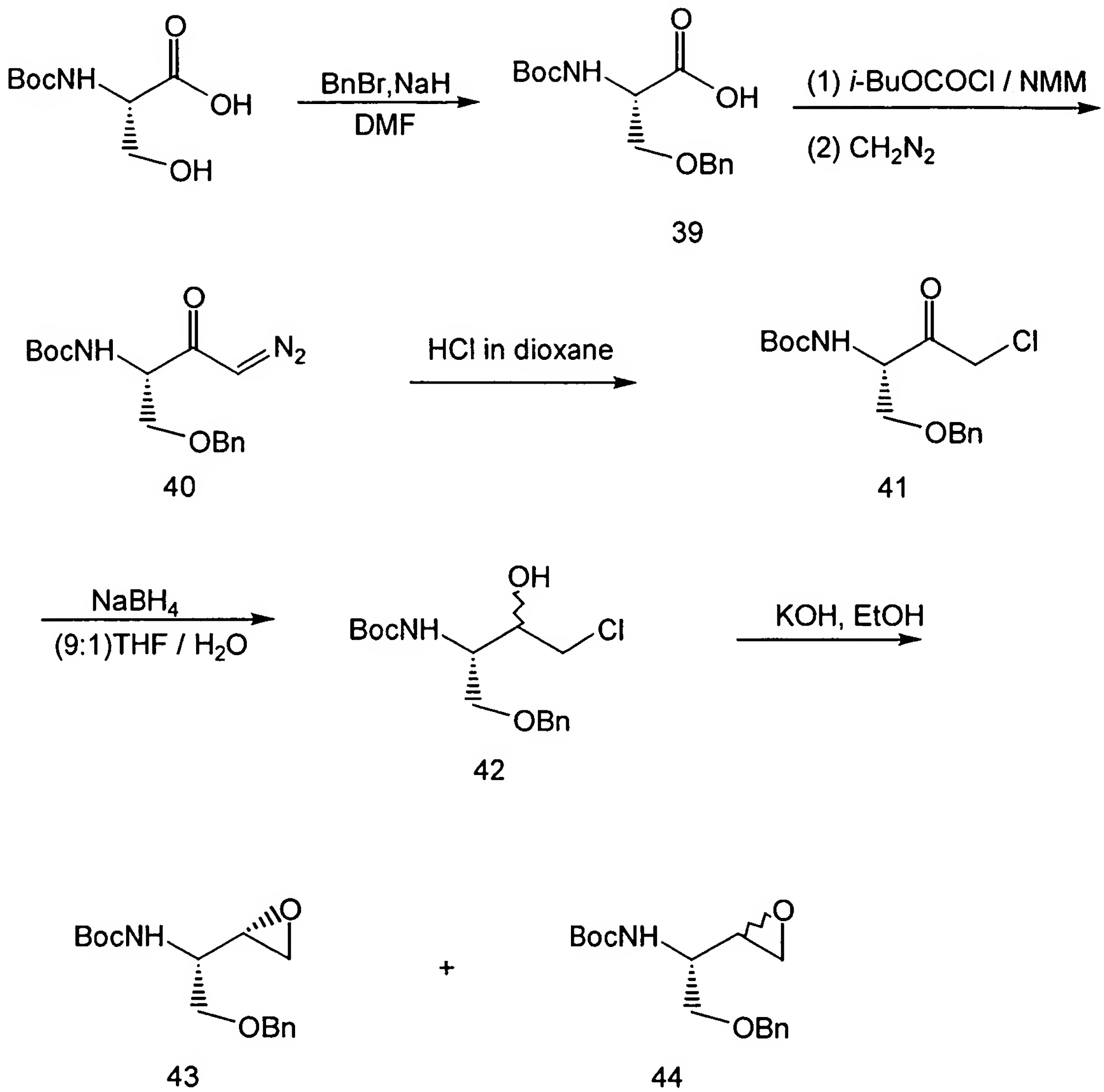
OH
H
N
O
OMe
S
NTf2, Cs2CO3
THF / CH2Cl2
OH
33
OTf
Pd(OAc)2, CO, dppp
Et3SiH, TEA, DMF
34
CHO
NaBH4
THF / H2O (9 / 1)
35

Scheme H11

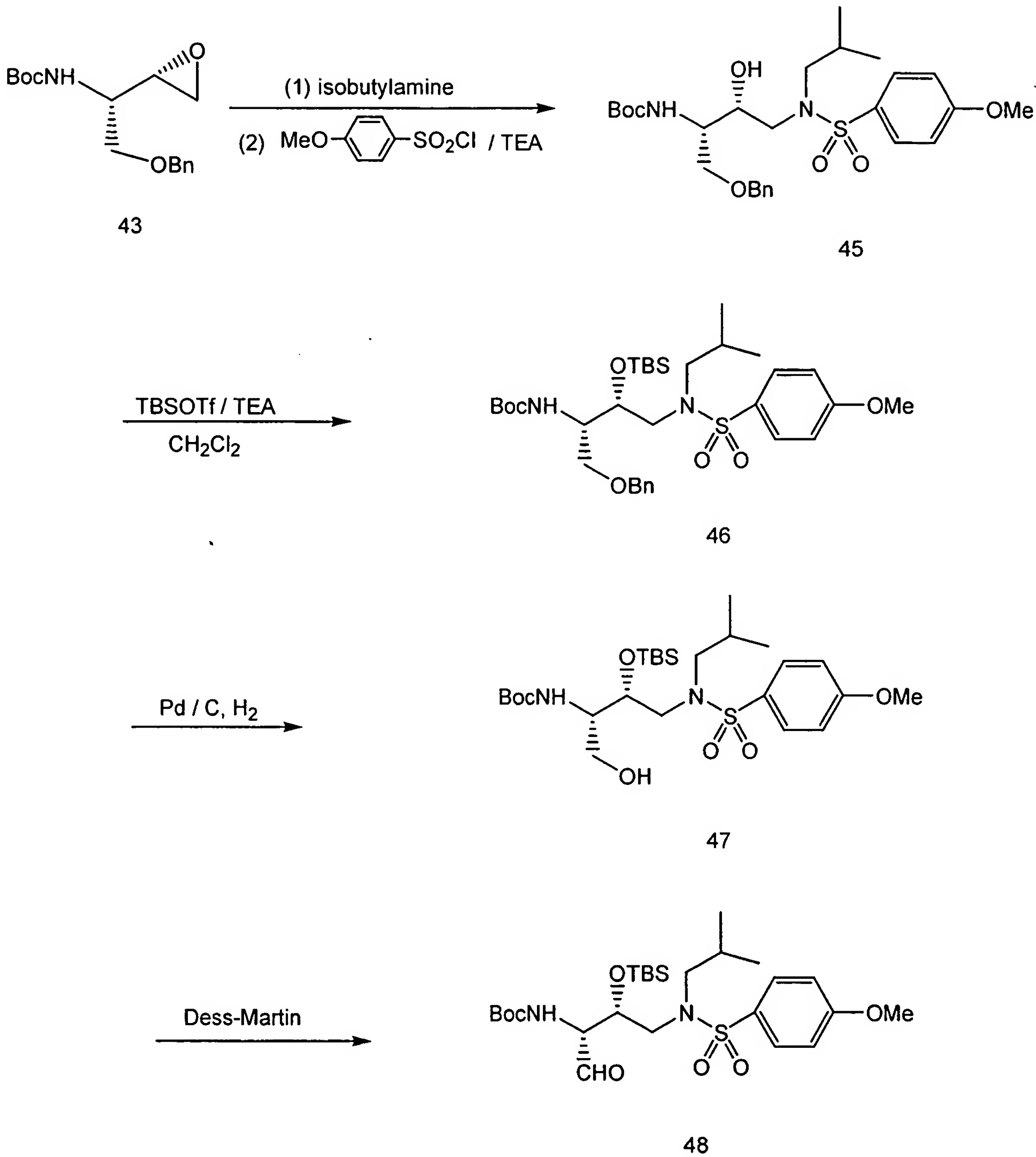


GS 191338

Scheme H12

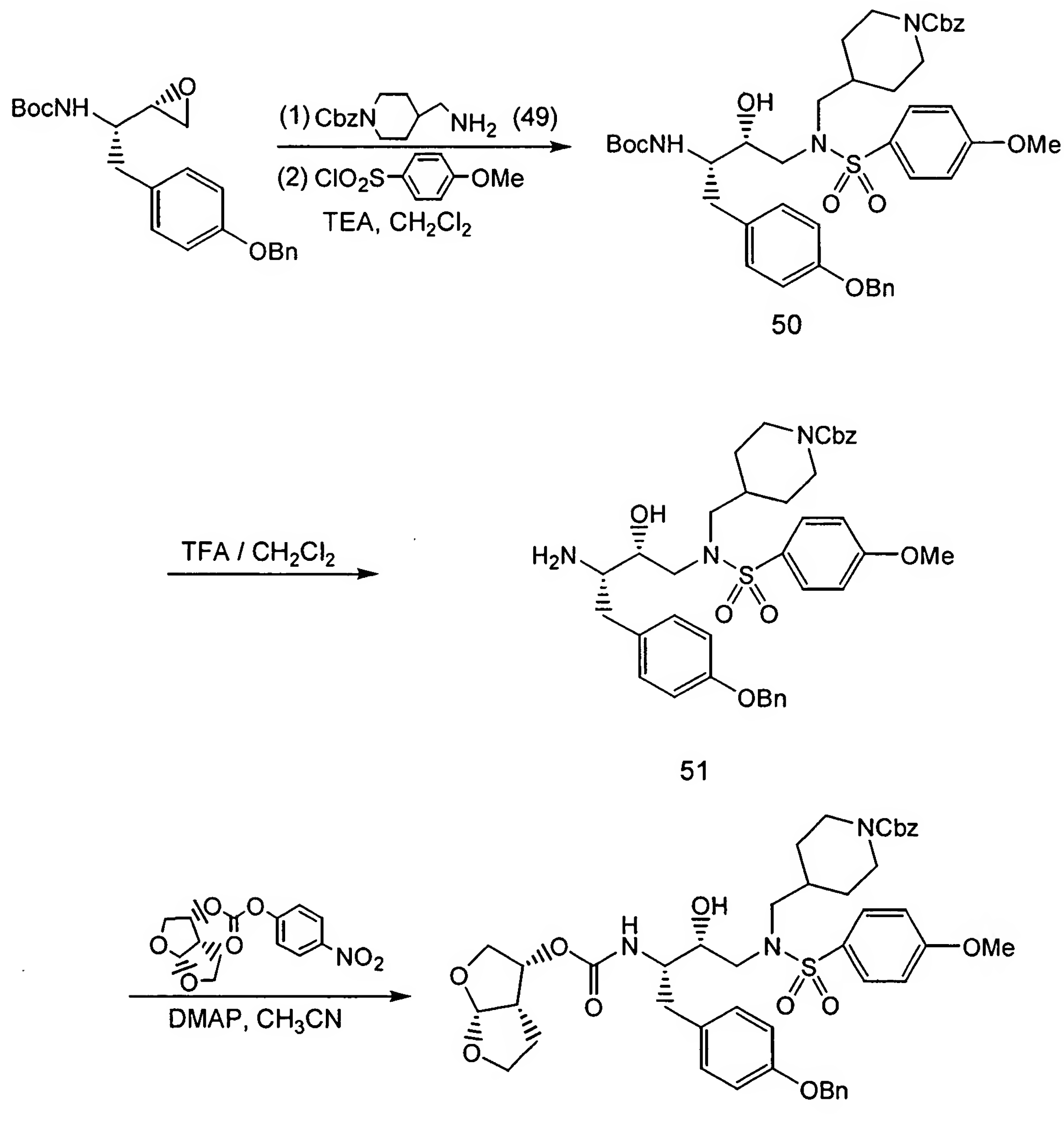

BocNH
OH
OH
BnBr,NaH
DMF
BocNH
OH
OBn
39
(1) i-BuOCOCl / NMM
(2) CH2N2
BocNH
N2
OBn
40
HCl in dioxane
BocNH
Cl
OBn
41
NaBH4
(9:1)THF / H2O
OH
BocNH
Cl
OBn
42
KOH, EtOH
BocNH
OBn
43
+
BocNH
OBn
44

Scheme H13



BocNH
OBn
43
(1) isobutylamine
(2) MeO SO2Cl / TEA
OH
OMe
45
TBSOTf / TEA
CH2Cl2
OTBS
46
Pd / C, H2
47
Dess-Martin
CHO
48

Scheme H14

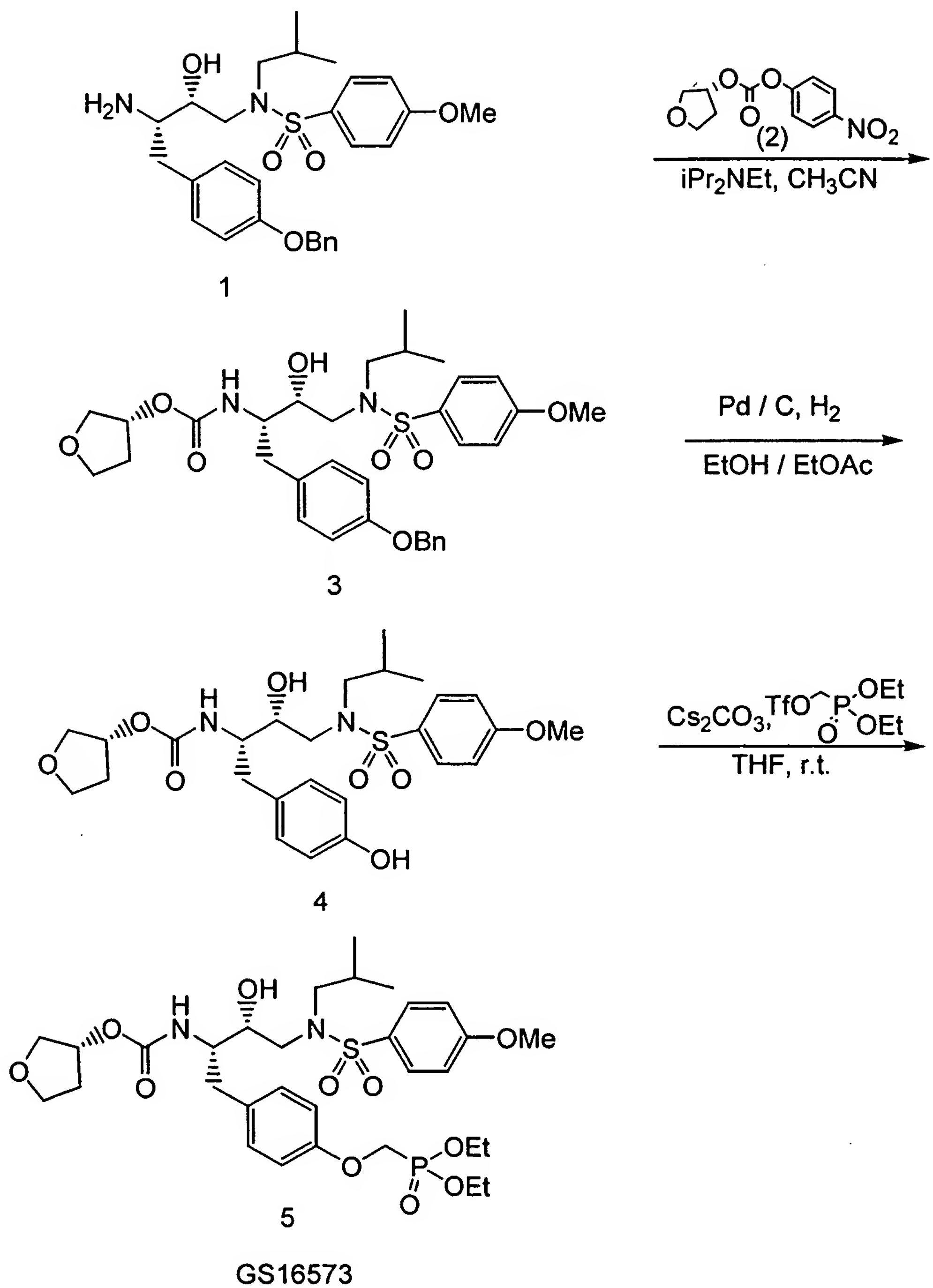


52

Scheme Section I

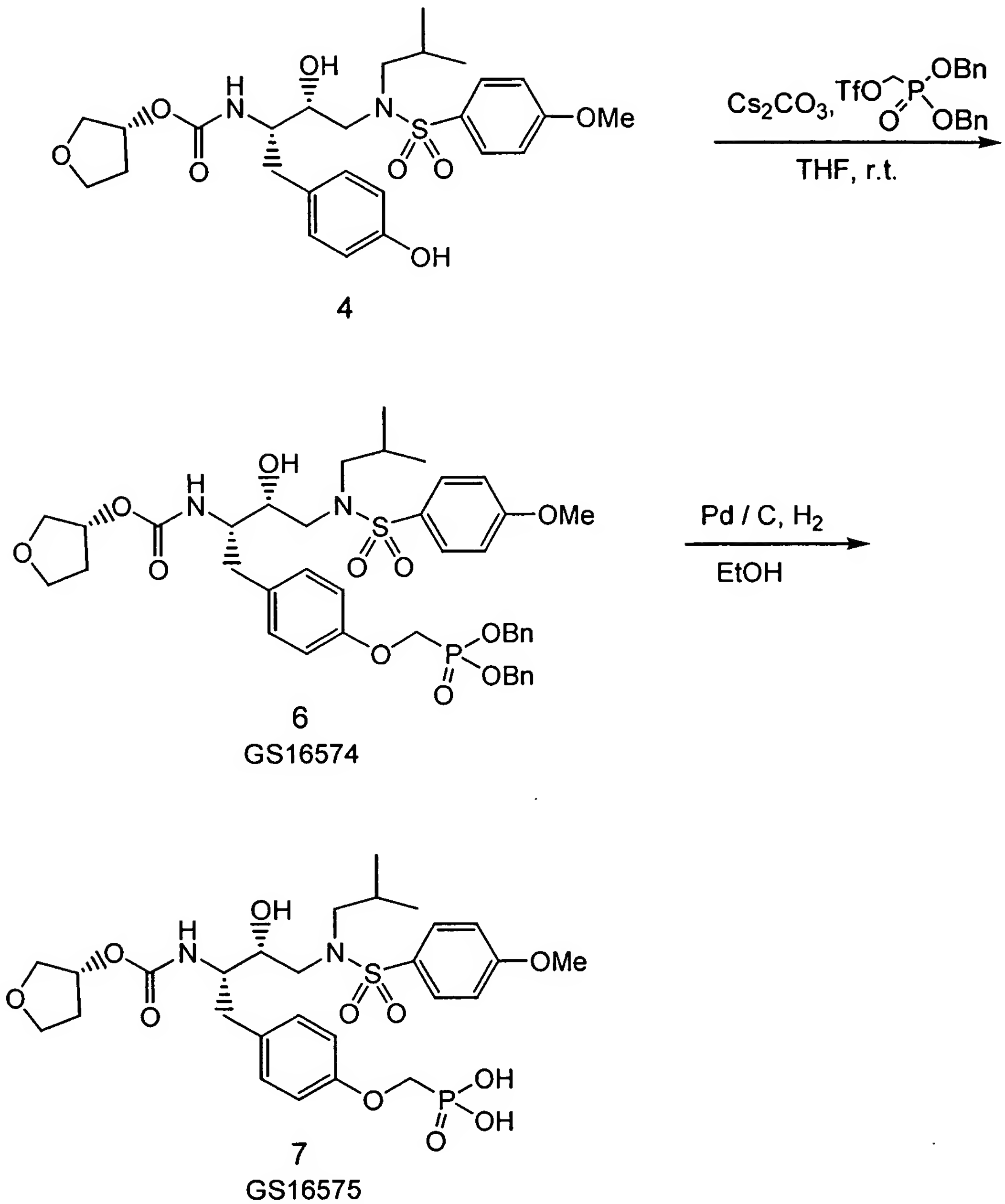
Schemes I1 to I3 are described in the examples.

Scheme I1

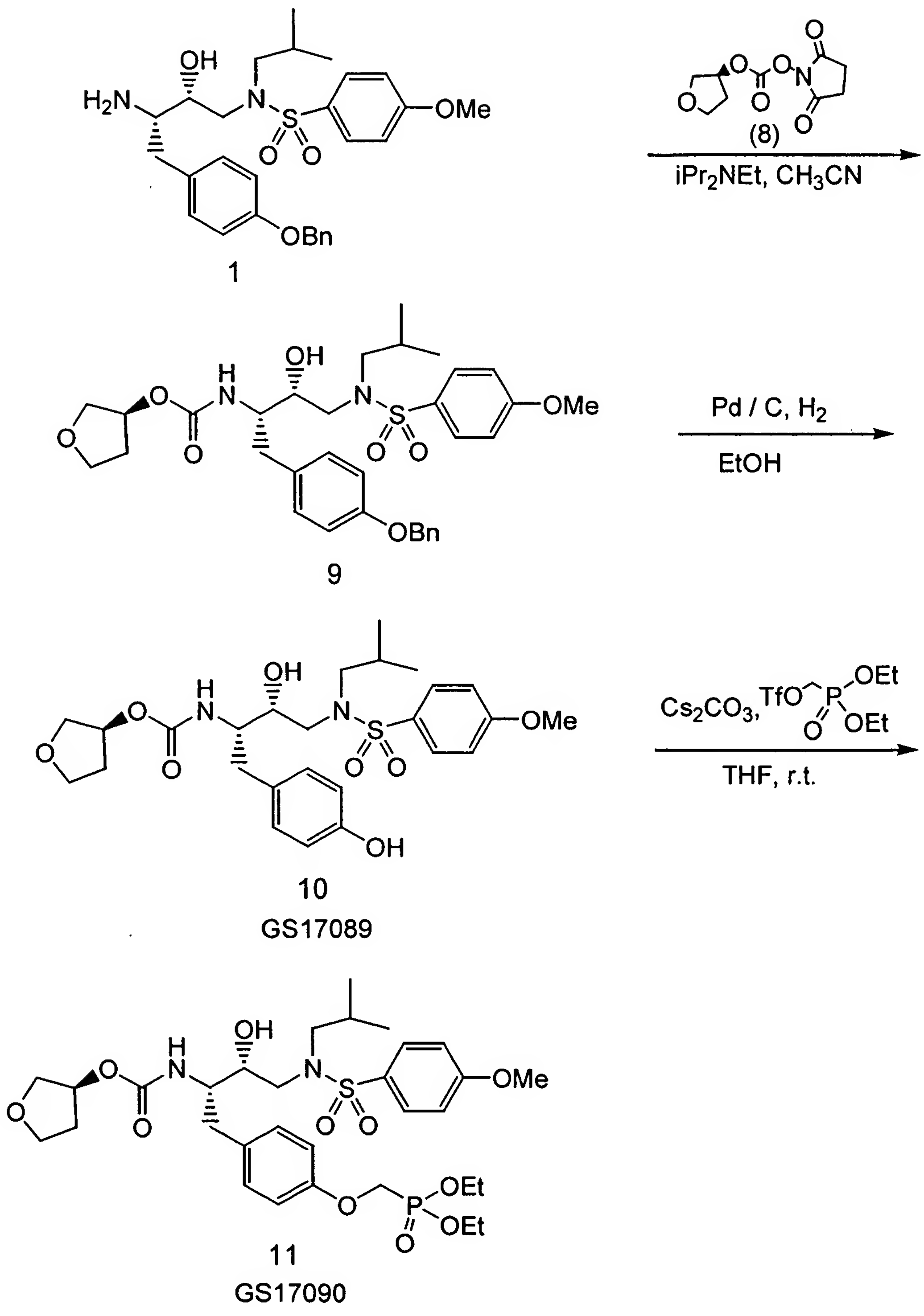


1
(2)
iPr2NEt, CH3CN
3
Pd / C, H2
EtOH / EtOAc
4
Cs2CO3, TfO
THF, r.t.
5
GS16573

Scheme I2


OH
H
N
O
O
N
S
O O
OMe
OH
Cs_2CO_3, TfO P OBn
O OBn
THF, r.t.
4
Pd / C, H_2
EtOH
6
GS16574
OBn
OBn
7
GS16575
OH
OH

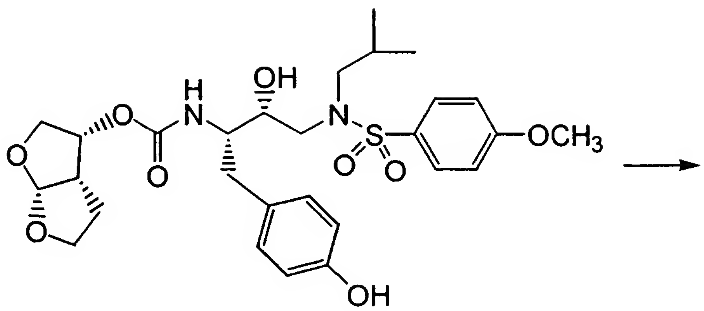
Scheme I3



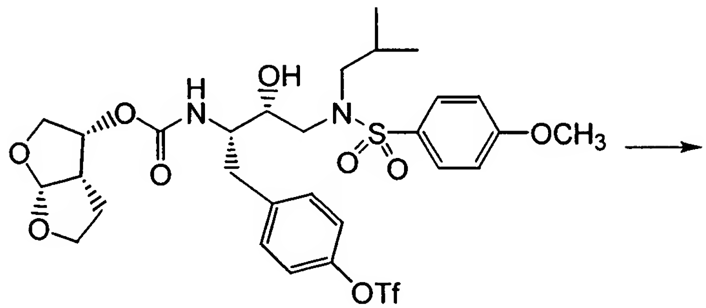
Scheme Section J

Schemes J1-J4 are described in the examples.

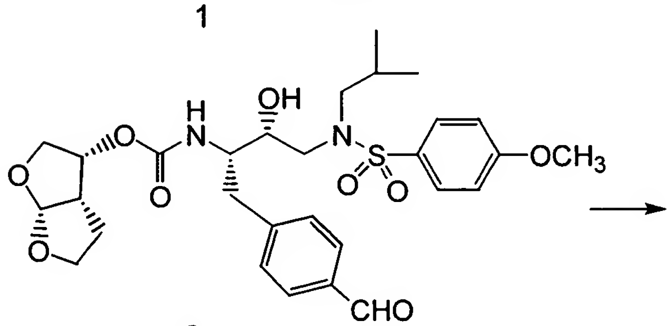
Scheme J1



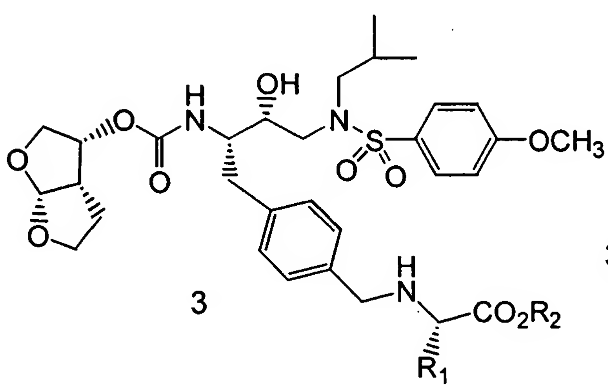
A



1



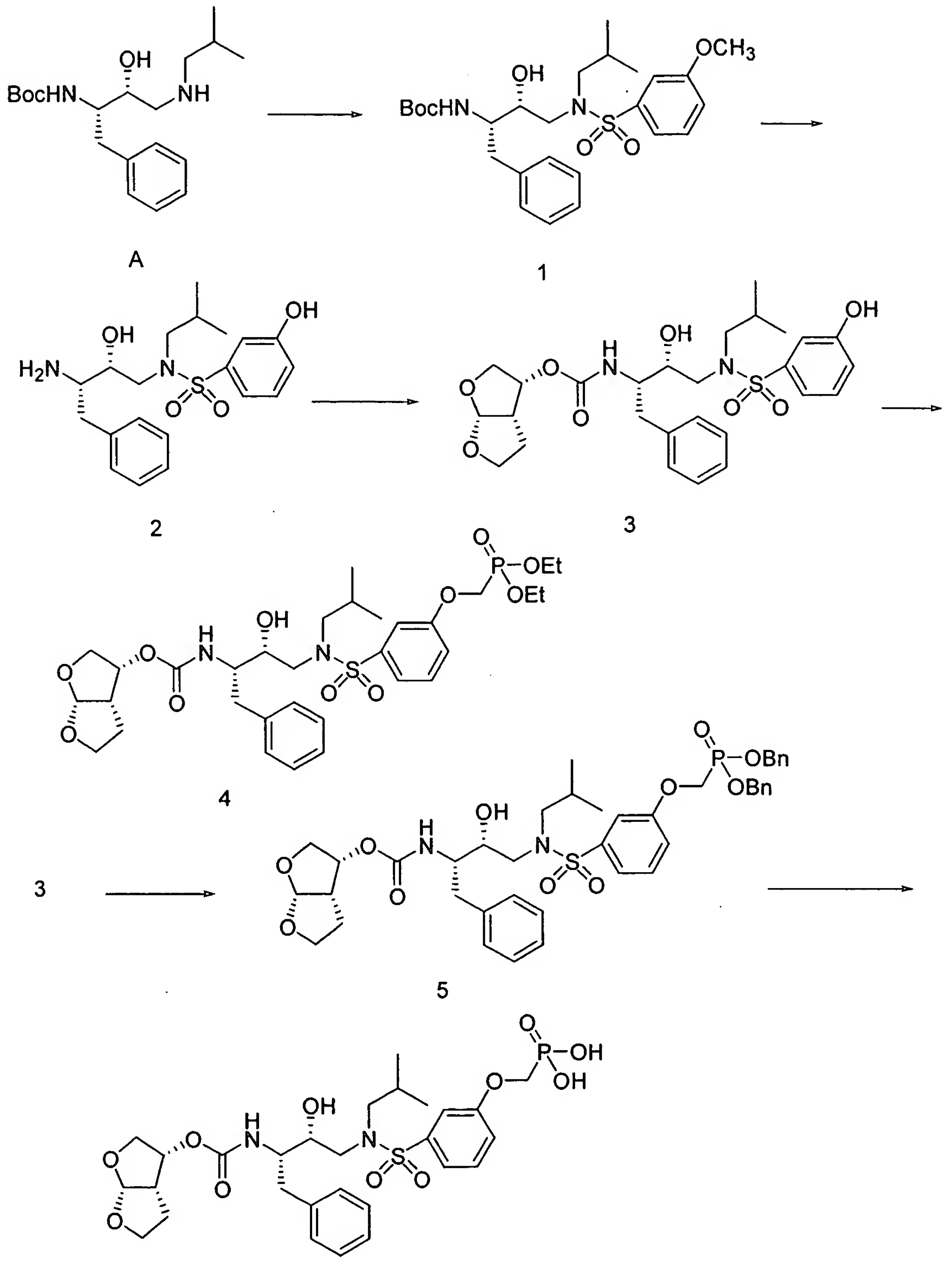
2



3a-e

3

Scheme J2



A

1

2

3

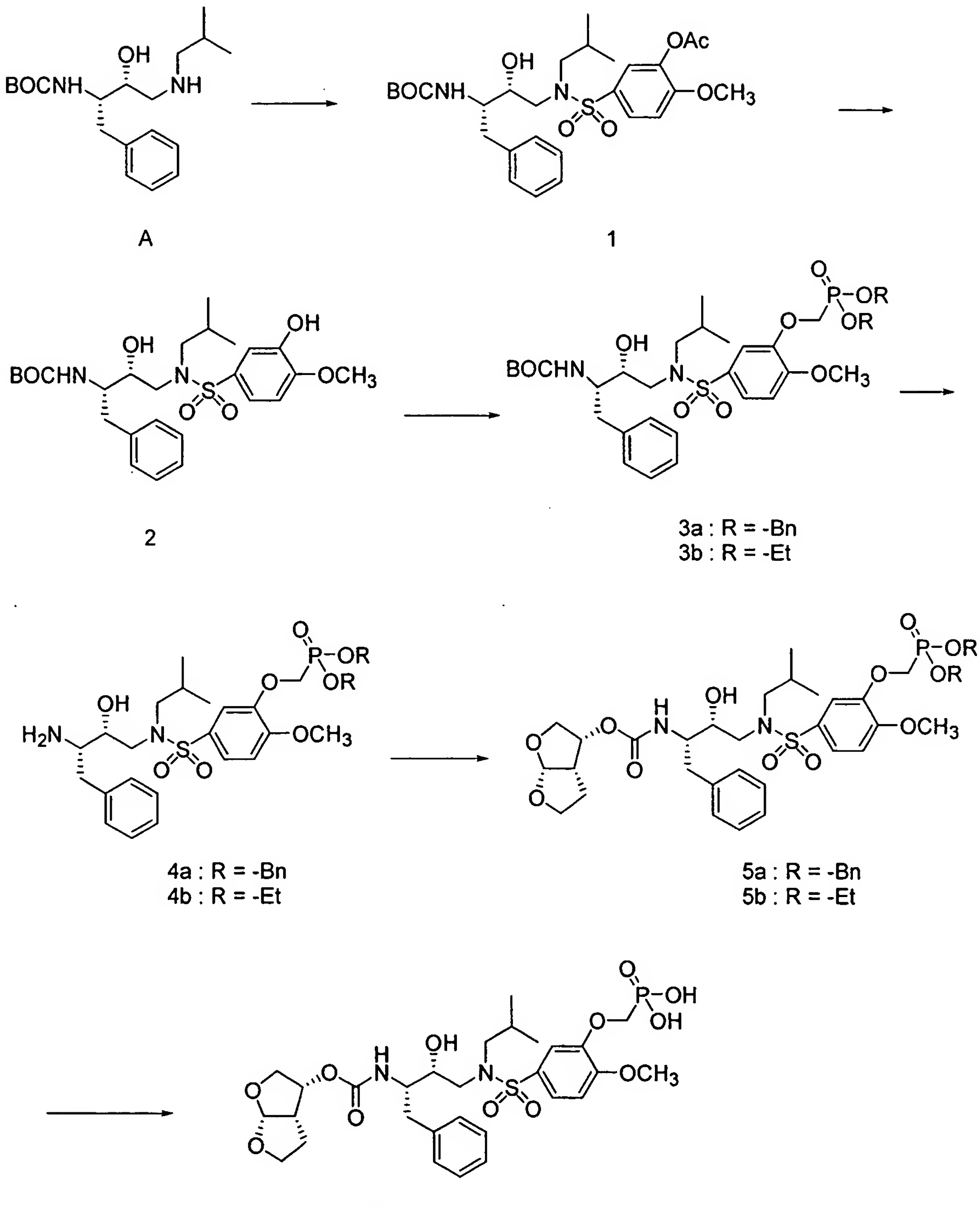
4

3

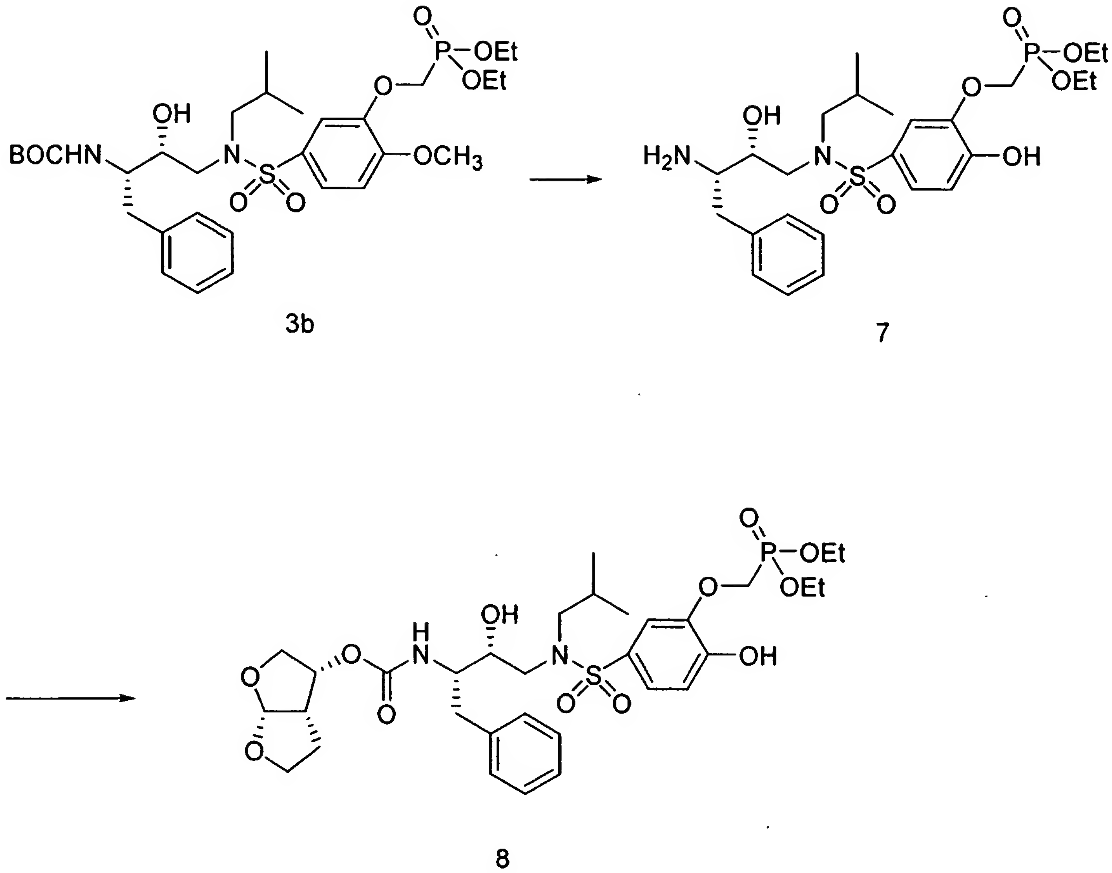
5

6

Scheme J3



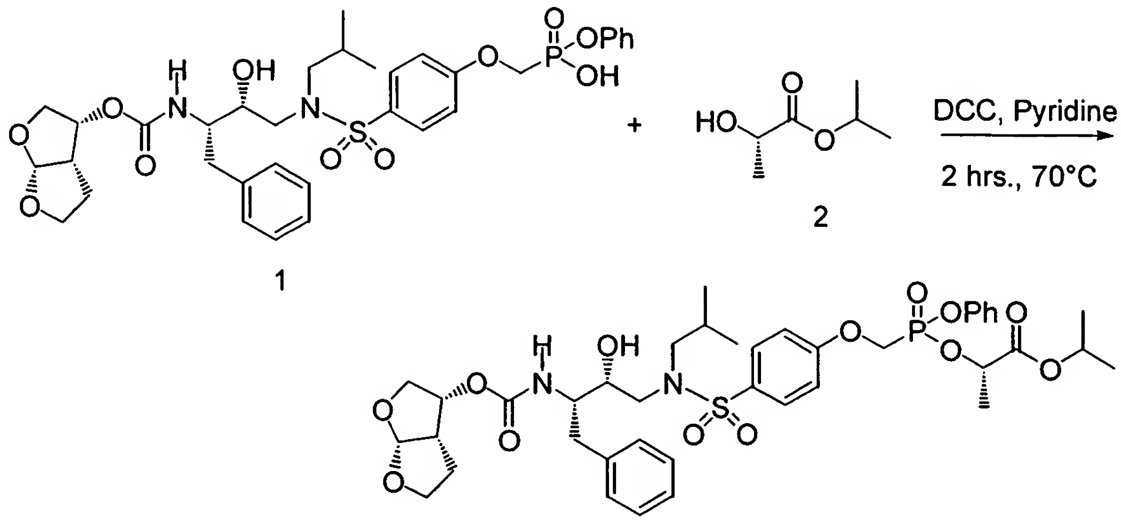
Scheme J4



<u>Scheme Section K</u>

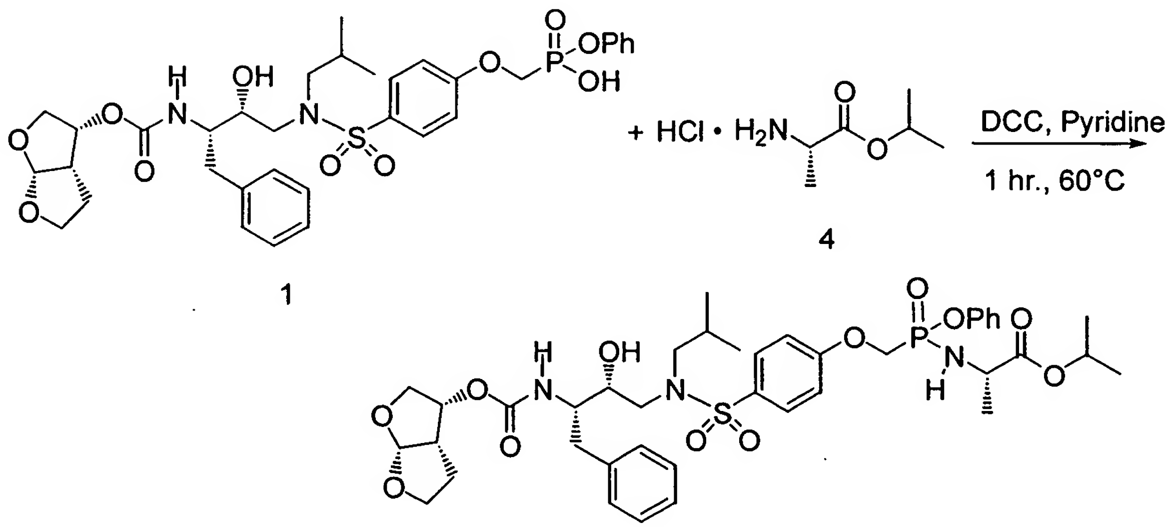
Schemes K1-K9 are described in the examples.

Scheme K1



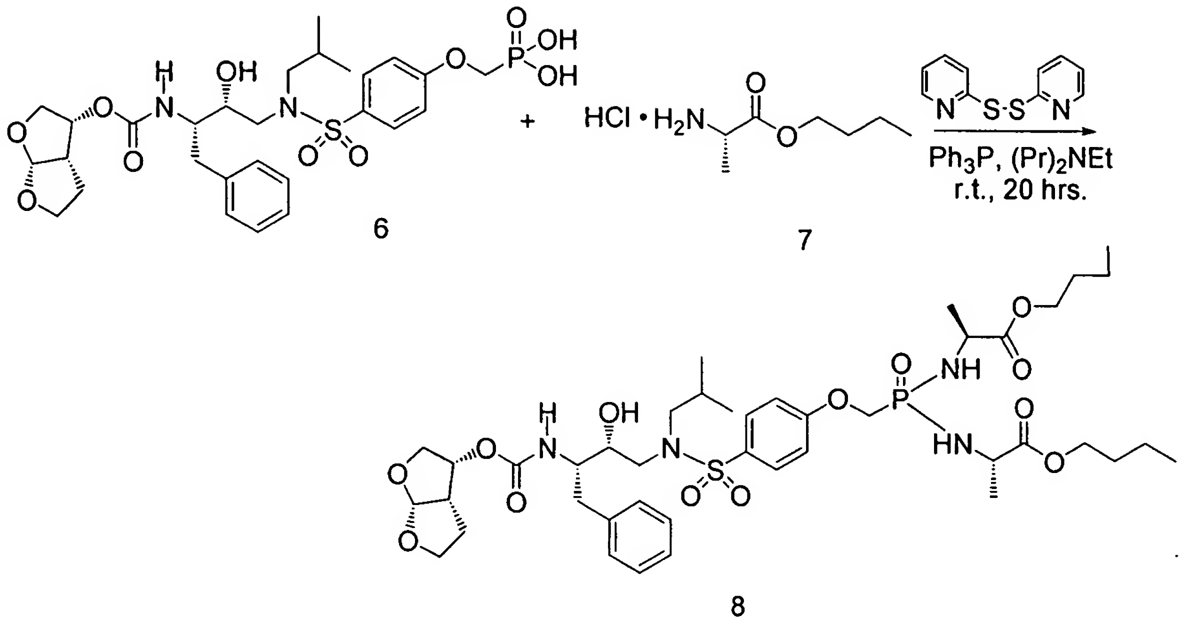
3

Scheme K2

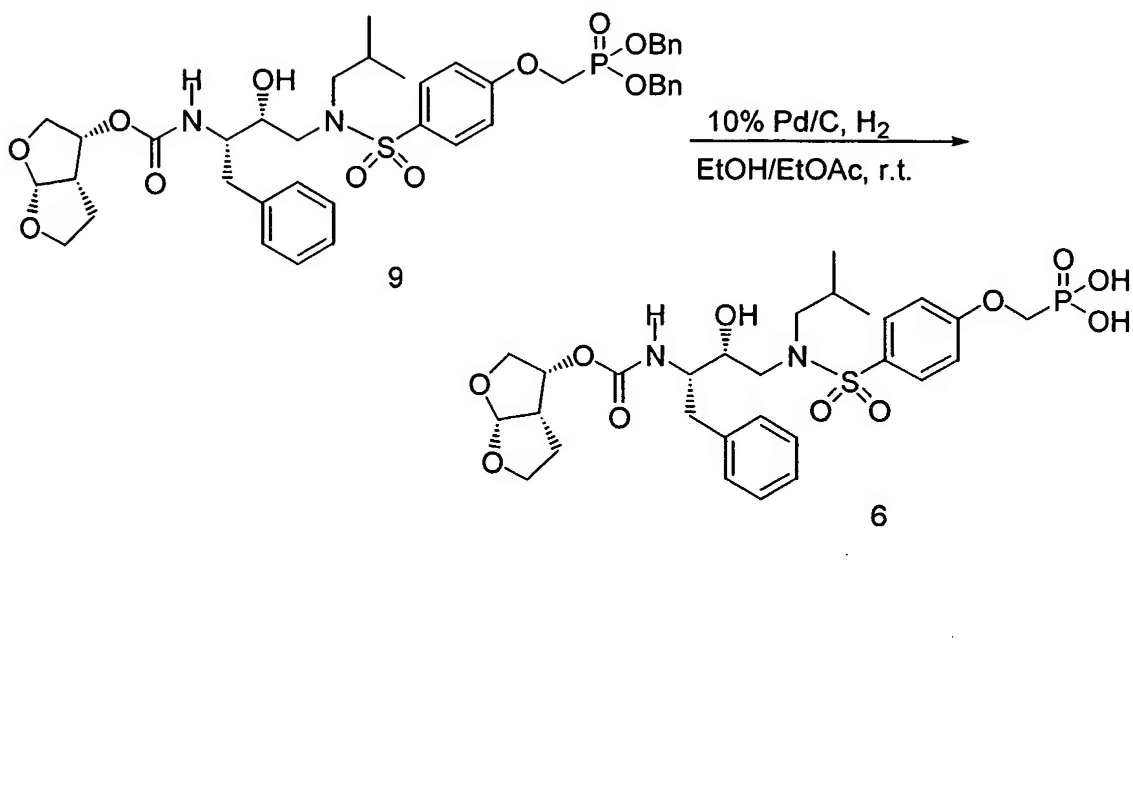


5

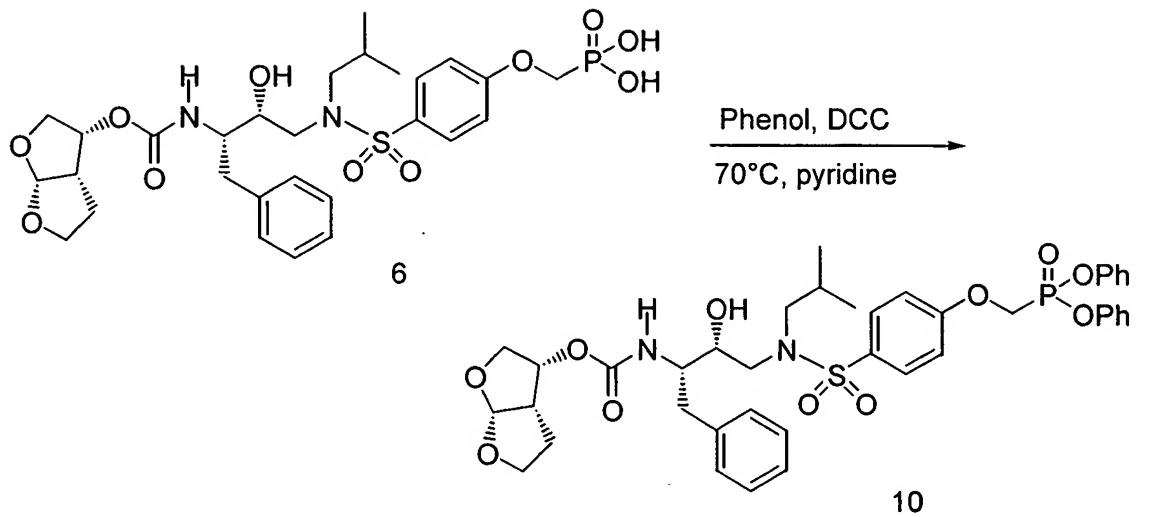
Scheme K3



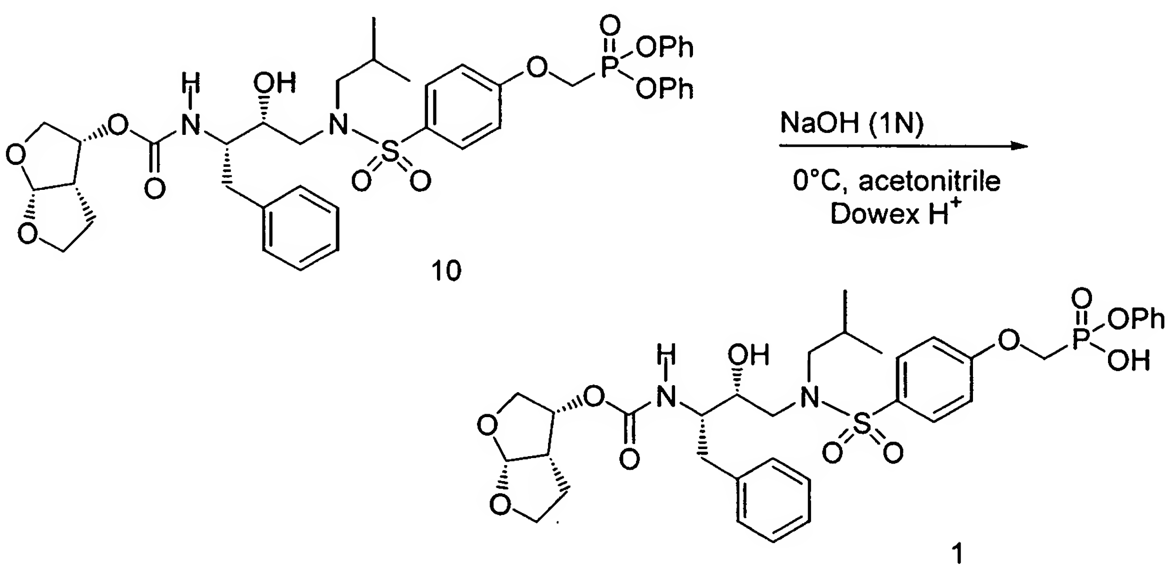
Scheme K4



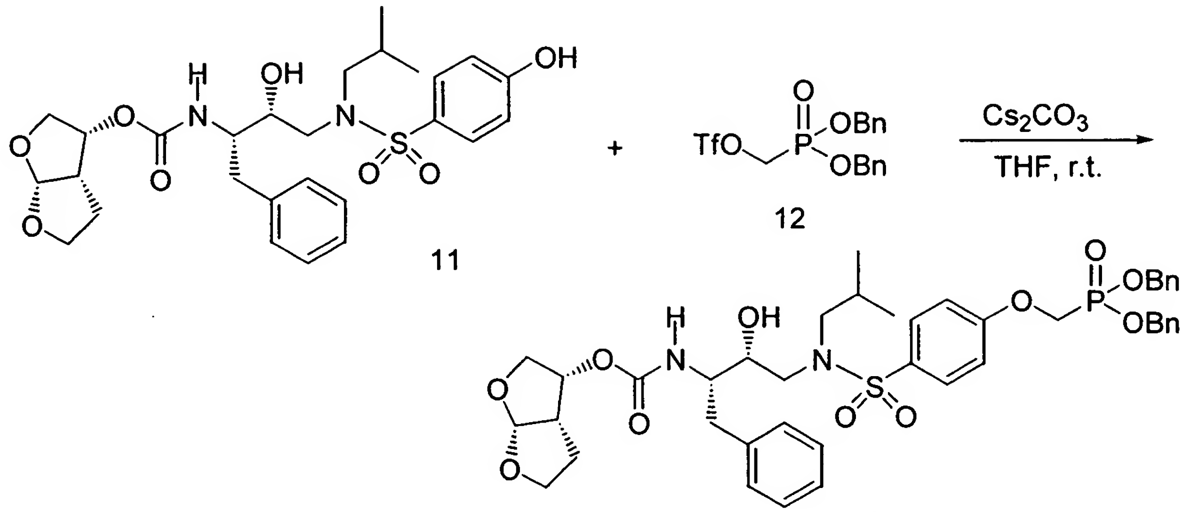
Scheme K5



Scheme K6



Scheme K7

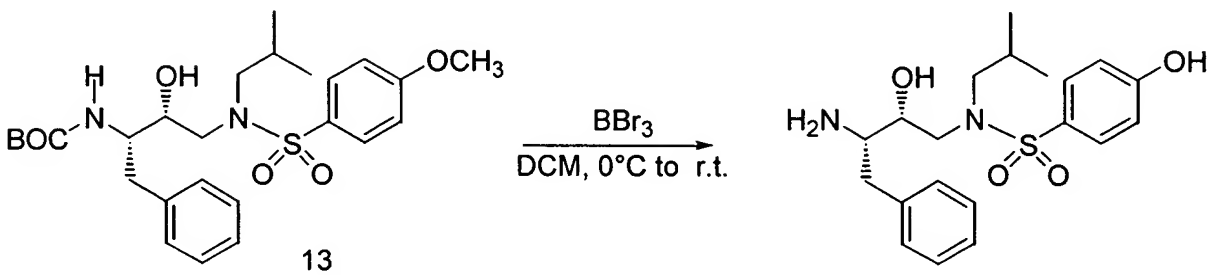


11

12

9

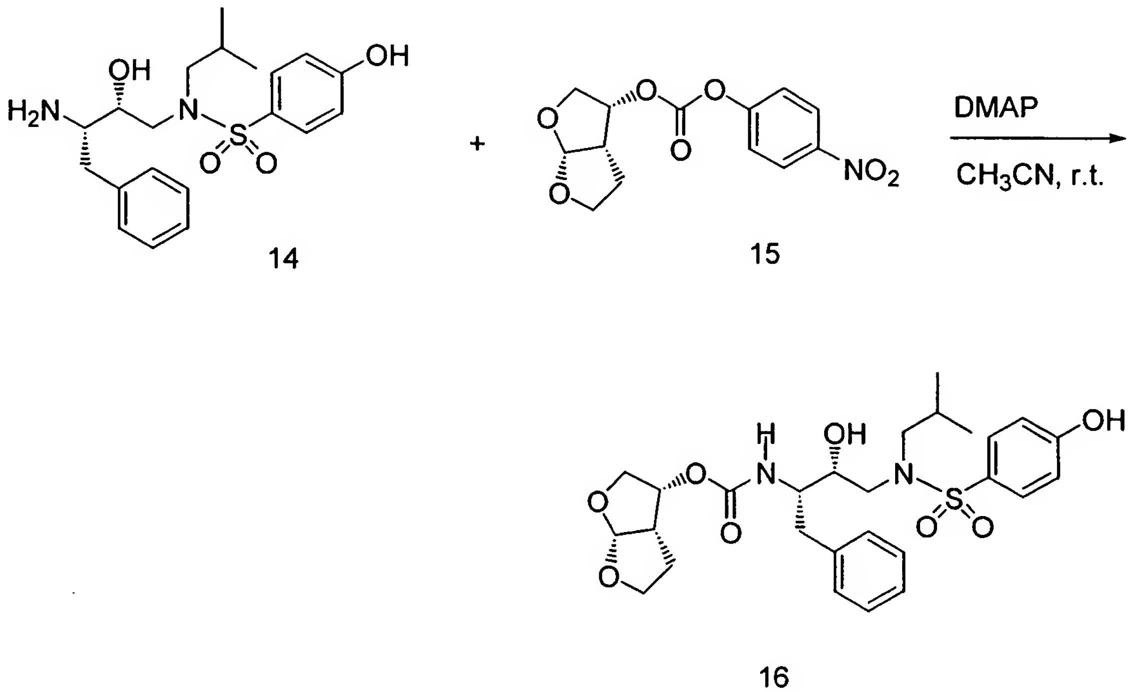
Scheme K8



13

14

Scheme K9

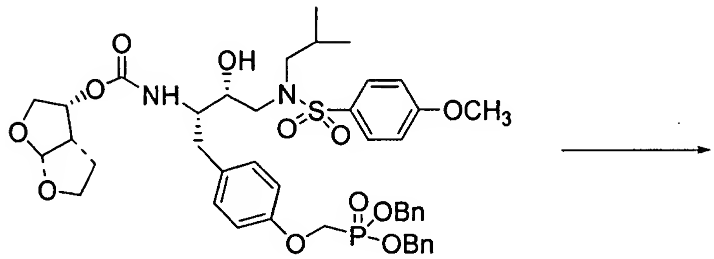


Scheme Section L

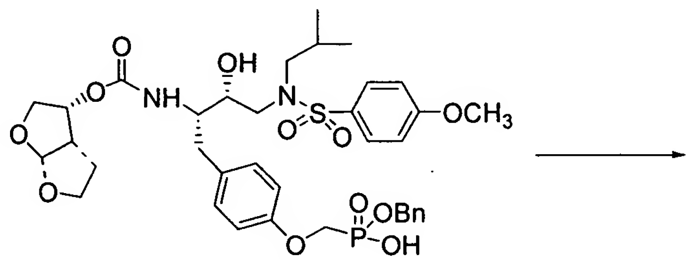
Schemes L1-L9 are described in the examples.

Scheme L1

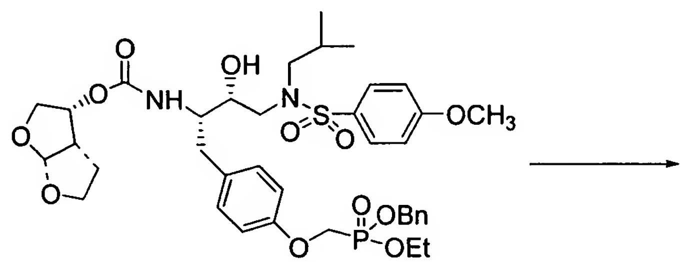
Synthesis of P1-Phosphonic ester



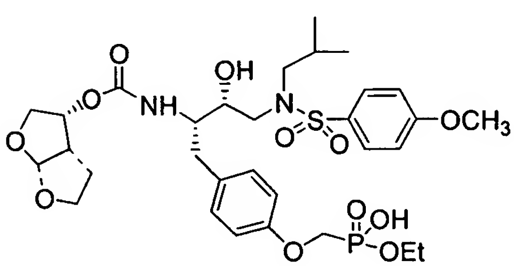
1



2

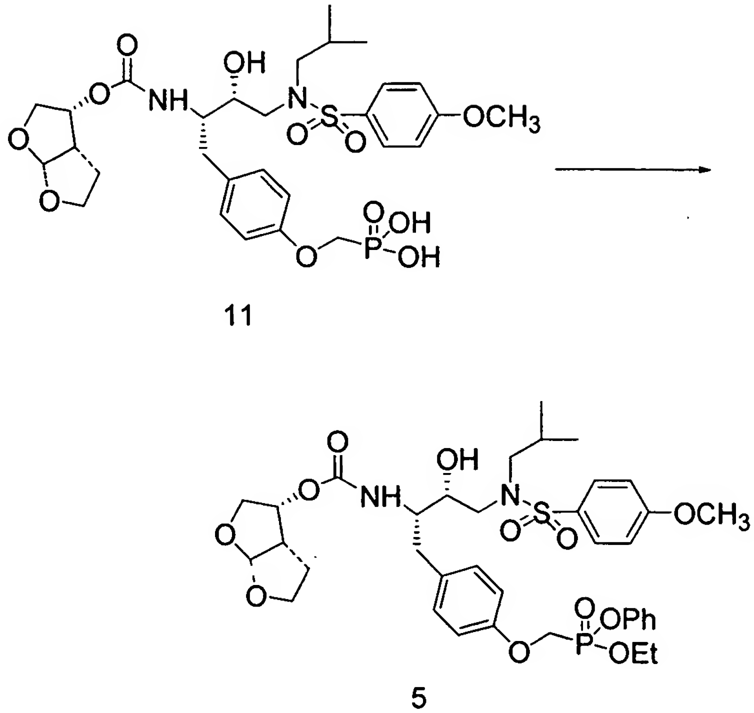


3

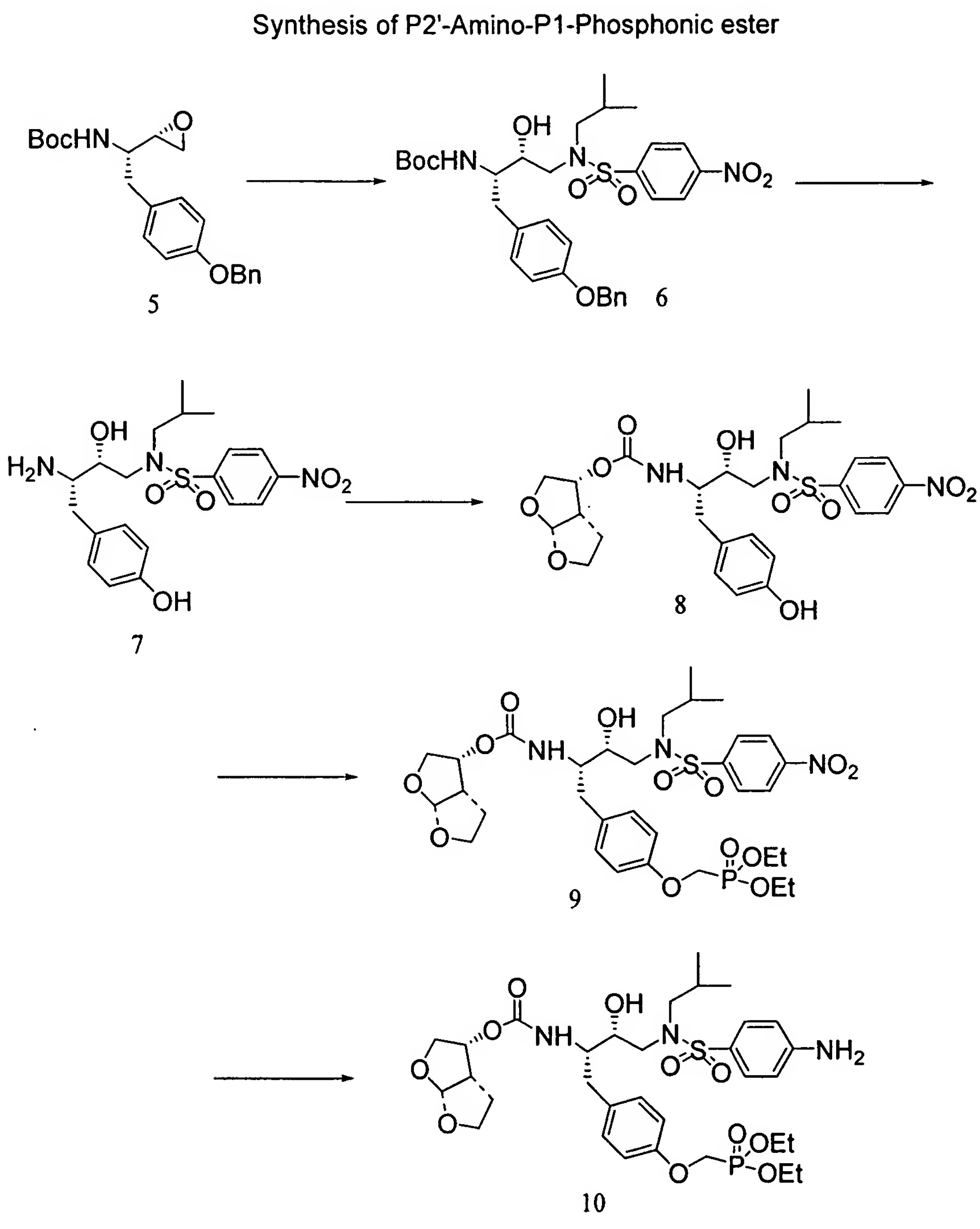


4

Scheme L2

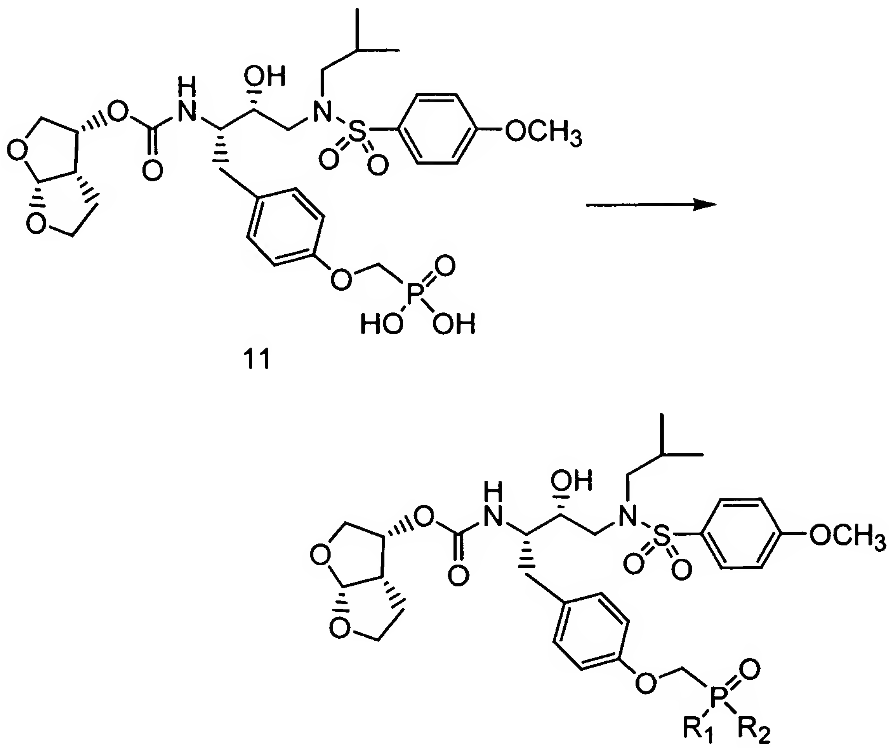


Scheme L3



Scheme L4

Synthesis of Bisamidates

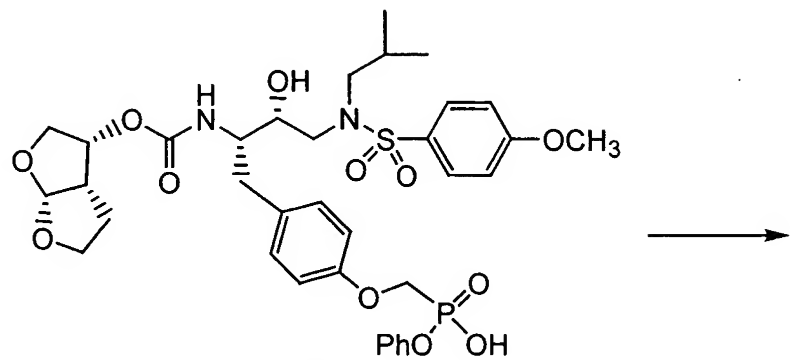


16 a,b,j and k

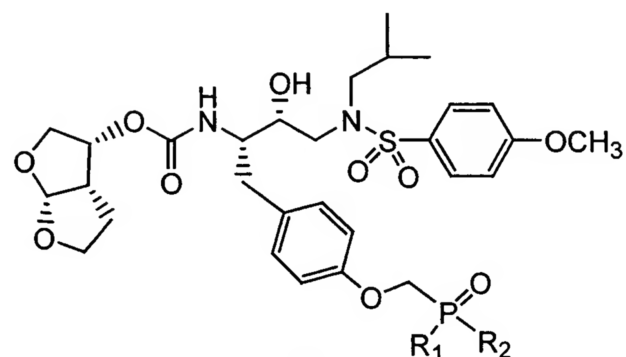
Compound	R_1	R_2
16a	Gly-Et	Gly-Et
16b	Gly-Bu	Gly-Bu
16j	Phe-Bu	Phe-Bu
16k	NHEt	NHEt

Scheme L5

Synthesis of Monoamidates



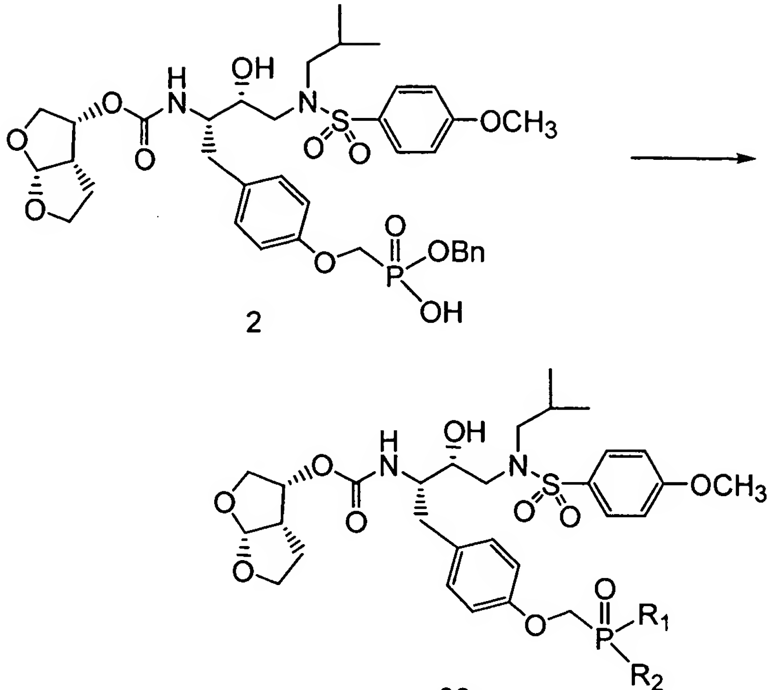
29



30

Compound	R_1	R_2
30a	OPh	Ala-Me
30b	OPh	Ala-Et
30c	OPh	(D)-Ala-iPr
30d	OPh	Ala-Bu
30e	OBn	Ala-Et

Scheme L6

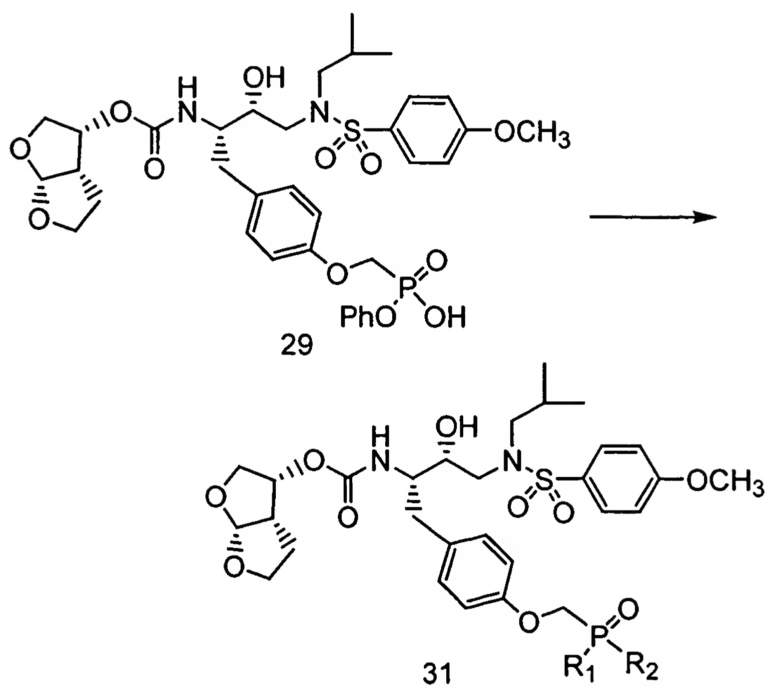


2

30e

Scheme L7

Synthesis of Lactates

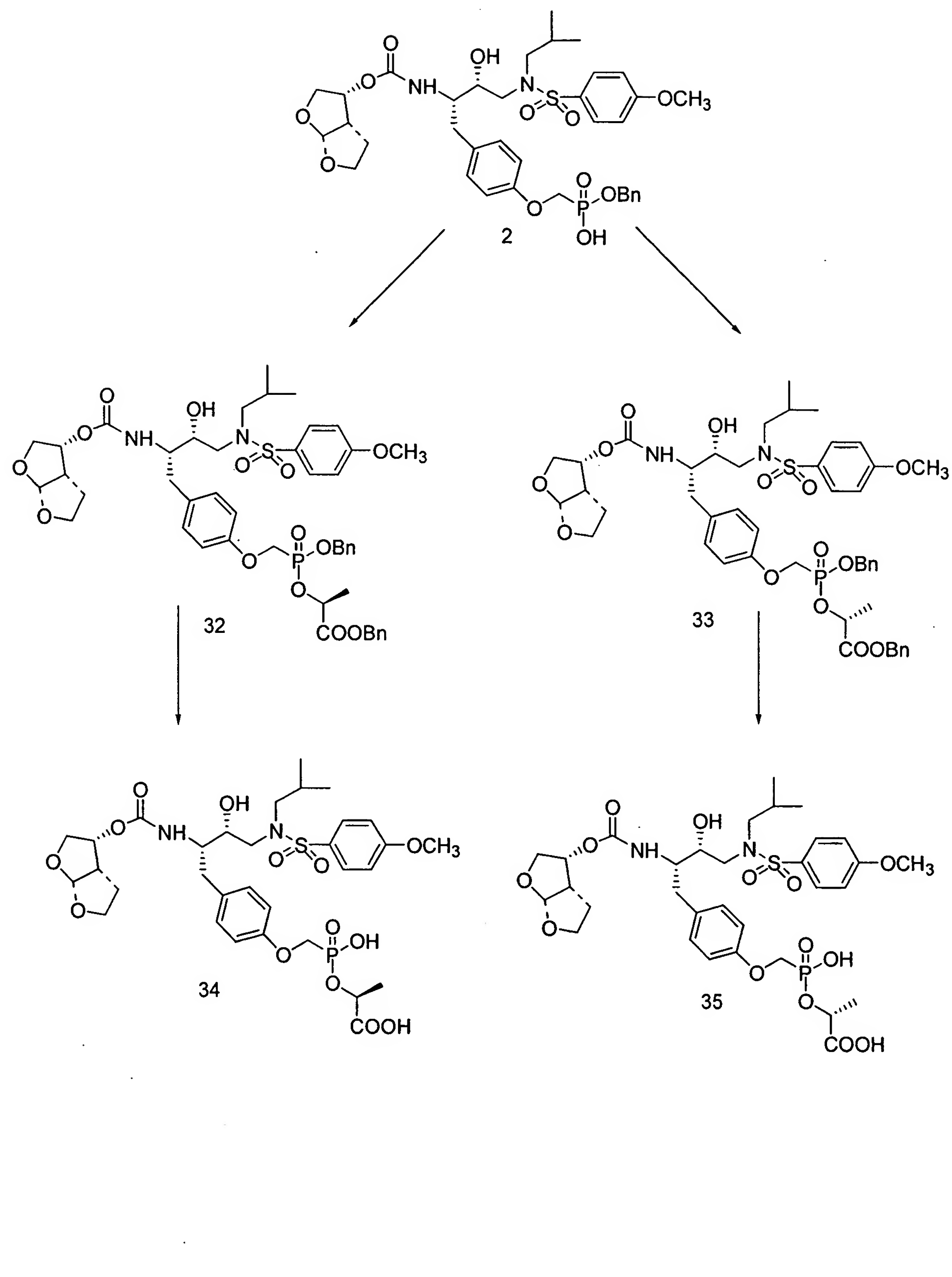


29

31

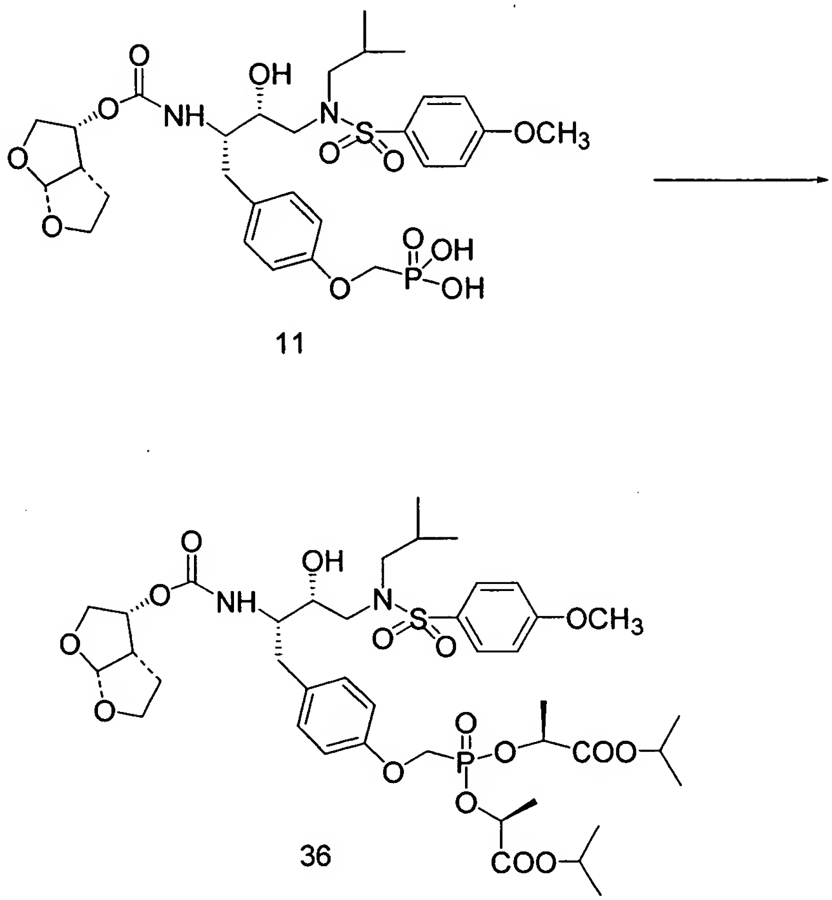
Compound	R_1	R_2
31a	OPh	Lac-iPr
31b	OPh	Lac-Et
31c	OPh	Lac-Bu
31d	OPh	(R)-Lac-Me
31e	OPh	(R)-Lac-Et

Scheme L8



Scheme L9

Synthesis of Bislactate



Examples

The following Examples refer to the Scheme Series A to L.

Some Examples have been performed multiple times. In repeated Examples, reaction conditions such as time, temperature, concentration and the like, and yields were within normal experimental ranges. In repeated Examples where significant modifications were made, these have been noted where the results varied significantly from those described. In Examples where different starting materials were used, these are noted. When the repeated Examples refer to a "corresponding" analog of a compound, such as a "corresponding ethyl ester", this intends that an otherwise present group, in this case typically a methyl ester, is taken to be the same group modified as indicated.

Example Section A

Example A1

Diazo ketone 1: To a solution of N-tert-Butoxycarbonyl-O-benzyl-L-tyrosine (11 g, 30 mmol, Fluka) in dry THF (55 mL) at -25-30°C (external bath temperature) was added isobutylchloroformate (3.9 mL, 30 mmol) followed by the slow addition of N.methylmorpholine (3.3 mL, 30 mmol). The mixture was stirred for 25 min, filtered while cold, and the filter cake was rinsed with cold (0°C) THF (50 mL). The filtrate was cooled to - 25°C and diazomethane (~50 mmol, generated from 15 g Diazald according to Aldrichimica Acta 1983, 16, 3) in ether (~150 mL) was poured into the mixed anhydride solution. The reaction was stirred for 15 min and was then placed in an icebath at 0°C, allowing the bath to warm to room temperature while stirring overnight for 15 h. The solvent was evaporated under reduced pressure and the residue was dissolved in EtOAc, washed with water, saturated $NaHCO_3$, saturated NaCl, dried ($MgSO_4$), filtered and evaporated to a pale yellow solid. The crude solid was slurried in hexane, filtered, and dried to afford the diazo ketone (10.9 g, 92%) which was used directly in the next step.

Example A2

Chloroketone 2: To a suspension of diazoketone 1 (10.8 g, 27 mmol) in ether (600 mL) at 0°C was added 4M HCl in dioxane (7.5 mL, 30 mmol). The solution was removed from the cooling bath, and allowed to warm to room temperature at which time the reaction was stirred 1 h. The reaction solvent was evaporated under reduced pressure to give a solid residue that was dissolved in ether and passed through a short column of silica gel. The solvent was evaporated to afford the chloroketone (10.7 g, 97%) as a solid.

Example A3

Chloroalcohol 3: To a solution of chloroketone 2 (10.6 g, 26 mmol) in THF (90 mL) was added water (10 mL) and the solution was cooled to 3-4°C (internal temperature). A solution of $NaBH_4$ (1.5 g, 39 mmol) in water (5 mL) was added dropwise over a period of 10 min. The mixture was stirred for 1h at 0°C and saturated $KHSO_4$ was slowly added until the pH<4 followed by saturated NaCl. The organic phase was washed with saturated NaCl, dried ($MgSO_4$) filtered and evaporated under reduced pressure. The crude product consisted of a 70:30 mixture of diastereomers by HPLC analysis (mobile phase, 77:25-CH_3CN:H_2O; flow rate: 1 mL/min;

detection: 254 nm; sample volume: 20 μL; column: 5μ C18, 4.6X250 mm, Varian; retention times: major diastereomer 3, 5.4 min, minor diastereomer 4, 6.1 min). The residue was recrystallized from EtOAc/hexane twice to afford the chloro alcohol 3 (4.86g, >99% diastereomeric purity by HPLC analysis) as a white solid.

Example A4

Epoxide 5: A solution of chloroalcohol 3 (4.32 g, 10.6 mmol) in EtOH (250 mL) and THF (100 mL) was treated with K_2CO_3 (4.4g, 325 mesh, 31.9 mmol) and the mixture was stirred for at room temperature for 20h. The reaction mixture was filtered and was evaporated under reduced pressure. The residue was partitioned between EtOAc and water and the organic phase was washed with saturated NaCl, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel to afford the epoxide (3.68 g, 94%) as a white solid.

Example A5

Sulfonamide 6: To a suspension of epoxide 5 (2.08 g, 5.6 mmol) in 2-propanol (20 mL) was added isobutylamine (10.7 mL, 108 mmol) and the solution was refluxed for 30 min. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH_2Cl_2 (20 mL) and cooled to 0°C. N,N'-diisopropylethylamine (1.96 mL, 11.3 mmol) was added followed by the addition of 4-methoxybenzenesulfonyl chloride (1.45 g, 7 mmol) in CH_2Cl_2 (5 mL) and the solution was stirred for 40 min at 0°C, warmed to room temperature and evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was recrystallized from EtOAc/hexane to give the sulfonamide (2.79 g, 81%) as a small white needles: mp 122-124°C (uncorrected).

Example A6

Carbamate 7: A solution of sulfonamide 6 (500 mg, 0.82 mmol) in CH_2Cl_2 (5 mL) at 0°C was treated with trifluoroacetic acid (5 mL). The solution was stirred at 0°C for 30 min and was removed from the cold bath stirring for an additional 30 min. Volatiles were evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic extracts were washed

with saturated NaCl, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was dissolved in CH_3CN (5 mL) and was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (263 mg, 0.89 mmol, prepared according to Ghosh *et al.*, *J. Med. Chem.* 1996, 39, 3278.) and N,N-dimethylaminopyridine (197 mg, 1.62 mmol). After stirring for 1.5h at room temperature, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 5% citric acid. The organic phase was washed twice with 1% K_2CO_3, and then was washed with saturated NaCl, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (1/1 -EtOAc/hexane) affording the carbamate (454 mg, 83%) as a solid: mp 128-129°C (MeOH, uncorrected).

Example A7

Phenol 8: A solution of carbamate 7 (1.15 g, 1.7 mmol) in EtOH (50 mL) and EtOAc (20 mL) was treated with 10% Pd/C (115 mg) and was stirred under H_2 atmosphere (balloon) for 18h. The reaction solution was purged with N_2, filtered through a 0.45 μM filter and was evaporated under reduced pressure to afford the phenol as a solid that contained residual solvent: mp 131-134°C (EtOAc/hexane, uncorrected).

Example A8

Dibenzylphosphonate 10: To a solution of dibenzylhydroxymethyl phosphonate (527 mg, 1.8 mmol) in CH_2Cl_2 (5 mL) was treated with 2,6-lutidine (300 μL, 2.6 mmol) and the reaction flask was cooled to -50°C (external temperature). Trifluoromethanesulfonic anhydride (360 μL, 2.1 mmol) was added and the reaction mixture was stirred for 15 min and then the cooling bath was allowed to warm to 0°C over 45 min. The reaction mixture was partitioned between ether and ice-cold water. The organic phase was washed with cold 1M H_3PO_4, saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford triflate 9 (697 mg, 91%) as an oil which was used directly without any further purification. To a solution of phenol 8 (775 mg, 1.3 mmol) in THF (5 mL) was added Cs_2CO_3 (423 mg, 1.3 mmol) and triflate 9 (710 mg, 1.7 mmol) in THF (2 mL). After stirring the reaction mixture for 30 min at room temperature additional Cs_2CO_3 (423 mg, 1.3 mmol) and triflate (178 mg, 0.33 mmol) were added and the mixture was stirred for 3.5h. The reaction mixture was evaporated under reduced pressure and the residue was partitioned between EtOAc and saturated NaCl. The

organic phase was dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was chromatographed on silica gel eluting (5% 2-propanol/CH_2Cl_2) to give the dibenzylphosphonate as an oil that solidified upon standing. The solid was dissolved in EtOAc, ether was added, and the solid was precipitated at room temperature overnight. After cooling to 0°C, the solid was filtered and washed with cold ether to afford the dibenzylphosphonate (836 mg, 76%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.66 (d, 2H), 7.31 (s, 10H), 7.08 (d, 2H), 6.94 (d, 2H), 6.76 (d, 2H), 5.59 (d, 1H), 5.15-4.89 (m, 6H), 4.15 (d, 2H), 3.94-3.62 (m, 10H), 3.13-2.69 (m, 7H), 1.78 (m, 1H), 1.70-1.44 (m, 2H), 0.89-0.82 (2d, 6H); ^{31}P NMR ($CDCl_3$) δ 18.7; MS (ESI) 853 (M+H).

Example A9

Phosphonic acid 11: A solution of dibenzylphosphonate 10 (0.81 g) was dissolved in EtOH/ EtOAc (30mL/10 mL), treated with 10% Pd/C (80 mg) and was stirred under H_2 atmosphere (balloon) for 1.5h. The reaction was purged with N_2, and the catalyst was removed by filtration through celite. The filtrate was evaporated under reduced pressure and the residue was dissolved in MeOH and filtered with a 0.45 μM filter. After evaporation of the filtrate, the residue was triturated with ether and the solid was collected by filtration to afford the phosphonic acid (634 mg, 99%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.77 (d, 2H), 7.19 (d, 2H), 7.09 (d, 2H), 6.92 (d, 2H), 5.60 (d, 1H), 4.95 (m, 1H), 4.17 (d, 2H), 3.94 (m, 1H), 3.89 (s, 3H), 3.85-3.68 (m, 5H), 3.42 (dd, 1H), 3.16-3.06 (m, 2H), 2.96-2.84 (m, 3H), 2.50 (m, 1H), 2.02 (m, 1H), 1.58 (m, 1H), 1.40 (dd, 1H), 0.94 (d, 3H), 0.89 (d, 3H); ^{31}P NMR ($CDCl_3$) δ 16.2; MS (ESI) 671 (M-H).

Example A10

Diethylphosphonate 13: Triflate 12 was prepared from diethyl hydroxymethylphosphonate (2g, 11.9 mmol), 2,6-lutidine (2.1 mL, 17.9 mmol), and trifluoromethanesulfonic anhydride (2.5 mL, 14.9 mmol) as described for compound 9. To a solution of phenol 8 (60 mg, 0.10 mmol) in THF (2 mL) was added Cs_2CO_3 (65mg, 0.20 mmol) and triflate 12 (45 mg, 0.15 mmol) in THF (0.25 mL). The mixture was stirred at room temperature for 2h and additional triflate (0.15 mmol) in THF (0.25 mL) was added. After 2h the reaction mixture was partitioned between EtOAc and saturated NaCl. The organic phase was dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was

chromatographed on silica gel (EtOAc) to give a residue that was purified by chromatography on silica gel (5% 2-propanol /CH_2Cl_2) to afford the diethylphosphonate as a foam: ^{1}H NMR ($CDCl_3$) δ 7.66 (d, 2H), 7.10 (d, 2H), 6.94 (d, 2H), 6.82 (d, 2H), 5.60 (d, 1H), 4.97 (d, 2H), 4.23-4.13 (m, 6H), 3.93-3.62 (m, 10H), 3.12-2.68 (m, 7H), 1.84-1.44 (m, 3H), 1.31 (t, 6H), 0.88-0.82 (2d, 6H); ^{31}P NMR ($CDCl_3$) δ 17.7; MS (ESI) 729 (M+H).

Example A11

Diphenylphosphonate 14: To a solution of 11 (100mg, 0.15 mmol) and phenol (141 mg, 1.5 mmol) in pyridine (1.5 mL) was added N, N-diisopropylcarbodiimide (50 μL, 0.38 mmol). The solution was stirred for 31h at room temperature and for 20h at 50°C. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel eluting (EtOAc) to provide diphenylphosphonate 14 (16 mg) as a foam: ^{31}P NMR ($CDCl_3$) δ 10.9; MS (ESI) 847 (M+Na).

Example A12

Bis-Poc-phosphonate 15: To a solution of 11 (50 mg, 0.74 mmol) and isopropylchloromethyl carbonate (29 mg, 0.19 mmol) in DMF (0.5 mL) was added triethylamine (26 μL, 0.19 mmol) and the solution was heated at 70°C (bath temperature) for 4.5h. The reaction was concentrated under reduced pressure and the residue was purified by preparative layer chromatography (2% 2-propanol/ CH_2Cl_2) to afford 15 (7 mg): ^{1}H NMR ($CDCl_3$) δ 7.71 (d, 2H), 7.15 (d, 2H); 7.01 (d, 2H), 6.93 (d, 2H), 5.80-5.71 (m, 4H), 5.67 (d, 1H), 5.07-4.87 (m, 4H), 4.35 (d, 2H), 4.04-3.68 (m, 10H), 3.13 (dd, 1H), 3.04-2.90 (m, 5H), 2.79 (dd, 1H), 1.88-1.50 (m, 3H+H_2O peak), 1.30 (m, 12H), 0.93 (d, 3H), 0.88 (d, 3H); ^{31}P NMR ($CDCl_3$) δ 19.6.

Example A13

Synthesis of Bisamidates 16a-j. Representative Procedure, Bisamidate 16f: A solution of phosphonic acid 11 (100 mg, 0.15 mmol) and (S)-2-aminobutyric acid butyl ester hydrochloride (116 mg, 0.59 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph_3P (117 mg, 0.45 mmol) and 2,2'-dipyridyl disulfide (98 mg, 0.45 mmol) in pyridine (1 mL) stirring for 20h at room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH_2Cl_2). The purified product was

suspended in ether and was evaporated under reduced pressure to afford bisamidate 16f (106 mg, 75%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.72 (d, 2H), 7.15 (d, 2H), 7.01 (d, 2H), 6.87 (d, 2H), 5.67 (d, 1H), 5.05 (m, 1H), 4.96 (d, 1H), 4.19-3.71 (m overlapping s, 18H,), 3.42 (t, 1H), 3.30 (t, 1H), 3.20 (dd, 1H), 3.20-2.97 (m, 4H), 2.80 (dd, 2H), 1.87-1.54 (m, 19H), 1.42-1.35 (4H), 0.97-0.88 (m, 18H); ^{31}P NMR ($CDCl_3$) δ 20.3; MS (ESI) 955 (M+H).

Compound	R_1	R_2	Amino Acid
16a	H	Et	Gly
16b	H	Bu	Gly
16c	Me	Et	Ala
16d	Me	Bu	Ala
16e	Et	Et	Aba[1]
16f	Et	Bu	Aba[1]
16g	iBu	Et	Leu
16h	iBu	Bu	Leu
16I	Bn	Et	Phe
16j	Bn	Bu	Phe

[1] Aba, 2-aminobutyric acid

Example A14

Diazo ketone 17: To a solution of N-tert-Butoxycarbonyl-p-bromo-L-phenylalanine (9.9 g, 28.8 mmol, Synthetech) in dry THF (55 mL) at -25-30°C (external bath temperature) was added isobutylchloroformate (3.74 mL, 28.8 mmol) followed by the slow addition of N-methylmorpholine (3.16 mL, 28.8 mmol). The mixture was stirred for 25 min, filtered while cold, and the filter cake was rinsed with cold (0°C) THF (50 mL). The filtrate was cooled to -25°C and diazomethane (~50 mmol, generated from 15 g diazald according to Aldrichimica Acta 1983, 16, 3) in ether (~150 mL) was poured into the mixed anhydride solution. The reaction was stirred for 15 min and was then placed in an icebath at 0°C, allowing the bath to warm to room temperature while stirring overnight for 15 h. The solvent was evaporated under reduced pressure and the residue was suspended in ether, washed with water, saturated $NaHCO_3$, saturated NaCl, dried ($MgSO_4$), filtered and evaporated to a pale yellow solid. The crude solid was slurried in hexane, filtered, and dried to afford diazo ketone 17 (9.73 g, 90%) which was used directly in the next step.

Example A15

Chloroketone 18: To a solution of diazoketone 17 (9.73 g, 26 mmol) in ether (500 mL) at 0°C was added 4M HCl in dioxane (6.6 mL, 26 mmol). The solution was stirred for 1 h at 0°C and 4M HCl in dioxane (1 mL) was added. After 1h, the reaction solvent was evaporated under reduced pressure to afford the chloroketone 18 (9.79 g, 98%) as a white solid.

Example A16

Chloroalcohol 19: A solution of chloroketone 18 (9.79g, 26 mmol) in THF (180 mL) and water (16 mL) was cooled to 0°C (internal temperature). Solid $NaBH_4$ (2.5 g, 66 mmol) was added in several portions over a period of 15 min while maintaining the internal temperature below 5°C. The mixture was stirred for 45 min and saturated $KHSO_4$ was slowly added until the pH<3. The mixture was partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc and the combined organic extracts were washed with brine, dried ($MgSO_4$) filtered and evaporated under reduced pressure. The residue was dissolved in EtOAc, and was passed through a short column of silica gel, and the solvent was evaporated. The solid residue was recrystallized from EtOAc/hexane to afford the chloroalcohol 19 (3.84g) as a white solid.

Example A17

Epoxide 21: A partial suspension of chloroalcohol 19 (1.16g, 3.1 mmol) in EtOH (50 mL) was treated with K_2CO_3 (2g, 14.5 mmol) and the mixture was stirred for 4 h at room temperature. The reaction mixture was diluted with EtOAc, filtered, and the solvents were evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl, and the organic phase was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to afford epoxide 21 (1.05g, 92%) as a white crystalline solid.

Example A18

Sulfonamide 22: To a solution of epoxide 21 (1.05g, 3.1 mmol) in 2-propanol (40 mL) was added isobutylamine (6 mL, 61 mmol) and the solution was refluxed for 30 min. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH_2Cl_2 (20 mL) and cooled to 0°C. Triethylamine (642 µL, 4.6 mmol) was added followed by the addition of (634 mg, 3.4 mmol) in CH_2Cl_2 (5 mL) and the solution was stirred for 2h at 0°C at which time the reaction solution was treated with additional triethylamine (1.5 mmol) and 4-

methoxybenzenesulfonyl chloride (0.31 mmol). After 1.5 h, the reaction solution was evaporated under reduced pressure. The residue was partitioned between EtOAc and cold 1M H_3PO_4. The organic phase was washed with saturated $NaHCO_3$, saturated NaCl, dried ($MgSO_4$), filtered and the solvent was evaporated under reduced pressure. The crude product was purified on silica gel (15/1 - CH_2Cl_2/EtOAc) to afford 1.67g of a solid which was recrystallized from EtOAc/hexane to give sulfonamide 22 (1.54g, 86%) as a white crystalline solid.

<u>Example A19</u>

Silyl ether 23: To a solution of the sulfonamide 22 (1.53g, 2.6 mmol) in CH_2Cl_2 (12 mL) at 0°C was added N,N-diisopropylethylamine (0.68 mL, 3.9 mmol) followed by tert-butyldimethylsilyl trifluoromethanesulfonate (0.75 mL, 3.3 mmol). The reaction solution was stirred for 1 h at 0°C and was warmed to room temperature, stirring for 17 h. Additional N,N-diisopropylethylamine (3.9 mmol) and tert-butyldimethylsilyl trifluoromethanesulfonate (1.6 mmol) was added, stirred for 2.5h, then heated to reflux for 3h and stirred at room temperature for 12 h. The reaction mixture was partitioned between EtOAc and cold 1M H_3PO_4. The organic phase was washed with saturated $NaHCO_3$, saturated NaCl, and was dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was purified on silica gel (2/1 - hexane/ether) to afford silyl ether 23 (780 mg, 43%) as an oil.

<u>Example A20</u>

Phosphonate 24: A solution of 23 (260 mg, 0.37 mmol), triethylamine (0.52 mL, 3.7 mmol), and diethylphosphite (0.24 mmol, 1.85 mmol) in toluene (2 mL) was purged with argon and to the solution was added $(Ph_3P)_4Pd$ (43 mg, 10 mol%). The reaction mixture was heated at 110°C (bath temperature) for 6 h, and was then allowed to stir at room temperature for 12h. The solvent was evaporated under reduced pressure and the residue was partitioned between ether and water. The aqueous phase was extracted with ether and the combined organic extracts were washed with saturated NaCl, dried ($MgSO_4$), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (2/1 - ethyl acetate/hexane) to afford diethylphosphonate 24 (153 mg, 55%).

Example A21

Phosphonic acid 26: To a solution of 24 (143 mg) in MeOH (5 mL) was added 4N HCl (2 mL). The solution was stirred at room temperature for 9h and was evaporated under reduced pressure. The residue was triturated with ether and the solid was collected by filtration to provide hydrochloride salt 25 (100 mg, 92%) as a white powder. To a solution of X (47 mg, 0.87 mmol) in CH_3CN (1 mL) at 0°C was added TMSBr (130 μL, 0.97 mmol). The reaction was warmed to room temperature and stirred for 6.5h at which time TMSBr (0.87 mmol) was added and stirring was continued for 16h. The solution was cooled to 0°C and was quenched with several drops of ice-cold water. The solvents were evaporated under reduced pressure and the residue was dissolved in several milliters of MeOH and treated with propylene oxide (2 mL). The mixture was heated to gentle boiling and evaporated. The residue was triturated with acetone and the solid was collected by filtration to give phosphonic acid 26 (32 mg, 76%) as a white solid.

Example A22

Phosphonate 27: To a suspension of 26 (32 mg, 0.66 mmol) in CH_3CN (1 mL) was added bis(trimethylsilyl)acetamide (100 μL, 0.40 mmol) and the solution was stirred for 30 min at room temperature. The solvent was evaporated under reduced pressure and the residue was dissolved in CH_3CN (1 mL). To this solution was added (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (20 mg, 0.069 mmol, prepared according to Ghosh *et al. J. Med. Chem.* 1996, 39, 3278.), N,N-diisopropylethylamine (35 μL, 0.20 mmol), and N,N-dimethylaminopyridine (catalytic amount). The solution was stirred for 22h at room temperature, diluted with water (0.5 mL) and was stirred with IR 120 ion exchange resin (325 mg, H^+ form) until the pH was <2. The resin was removed by filtration, washed with methanol and the filtrate was concentrated under reduced pressure. The residue was dissolved water, treated with solid $NaHCO_3$ until pH=8 and was evaporated to dryness. The residue was dissolved in water and was purified on C18 reverse phase chromatography eluting with water followed by 5%, 10% and 20% MeOH in water to give the disodium salt 27 (24 mg) as a pale yellow solid: ^1H NMR (D_2O) δ 7.72 (d, 2H), 7.52 (dd, 2H), 7.13 (dd, 2H), 7.05 (d, 2H), 5.58 (d, 1H), 4.87 (m, 1H), 3.86-3.53 (m overlapping s, 10H), 3.22 (dd, 1H), 3.12-2.85 (6H), 2.44 (m,

1H), 1.83 (m, 1H), 1.61 (m, 1H)1.12 (dd, 1H), 0.77 (m, 6H); ^{31}P NMR (D_2O) δ 11.23 ; MS (ESI) 641 (M-H).

Example A23

Diethylphosphonate 28: To a solution of 25 (16 mg, 0.028 mmol) in CH_3CN (0.5 mL) was added (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (9 mg, 0.031 mmol), N,N-diisopropylethylamine (20 μL, 0.11 mmol), and N,N-dimethylaminopyridine (catalytic amount). The solution was stirred at room temperature for 48 h and was then concentrated under reduced pressure. The residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic phase was washed with saturated $NaHCO_3$, saturated NaCl, and was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (2.5-5% 2-propanol/CH_2Cl_2). The residue obtained was further purified by preparative layer chromatography (5% MeOH/CH_2Cl_2) followed by column chromatography on silica gel (10% 2-propanol/CH_2Cl_2) to afford diethylphosphonate 28 (7 mg) as a foam: ^{1}H NMR ($CDCl_3$) δ 7.72-7.66 (m, 4H), 7.32-7.28 (2H), 6.96 (d, 2H), 5.60 (d, 1H), 4.97 (m, 2H), 4.18-4.01 (m, 4H), 3.94-3.60 (m overlapping s, 10H), 3.15-2.72 (m, 7H), 1.78 (m, 1H), 1.61 (m+H_2O, ~3H), 1.28 (t; 6H), 0.86 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 18.6 ; MS (ESI) 699 (M+H).

Prospective Example A24

Diphenyl phosphonate 14 is treated with aqueous sodium hydroxide to provide monophenyl phosphonate 29 according to the method found in *J. Med. Chem.* 1994, 37, 1857. Monophenyl phosphonate 29 is then converted to the monoamidate 30 by reaction with an amino acid ester in the presence of Ph_3 and 2,2'-dipyridyl disulfide as described in the synthesis of bisamidate 16f. Alteratively, monoamidate 30 is prepared by treating 29 with an amino acid ester and DCC. Coupling conditions of this type are found in *Bull. Chem. Soc. Jpn.* 1988, 61, 4491.

Example A25

Diazo ketone 1: To a solution of N-tert-Butoxycarbonyl-O-benzyl-L-tyrosine (25 g, 67 mmol, Fluka) in dry THF (150 mL) at -25-30°C (external bath temperature) was added isobutylchloroformate (8.9 mL, 69 mmol) followed by the slow addition of N.methylmorpholine

(37.5 mL, 69 mmol). The mixture was stirred for 40 min, and diazomethane (170 mmol, generated from 25 g 1-methyl-3-nitro-1-nitroso-guanidine according to Aldrichimica Acta 1983, 16, 3) in ether (400 mL) was poured into the mixed anhydride solution. The reaction was stirred for 15 min allowing the bath to warm to room temperature while stirring overnight for 4 h. The mixture was bubbled with N_2 for 30 min., washed with water, saturated $NaHCO_3$, saturated NaCl, dried ($MgSO_4$), filtered and evaporated to a pale yellow solid. The crude solid was slurried in hexane, filtered, and dried to afford the diazo ketone (26.8 g, 99%) which was used directly in the next step.

Example A26

Chloroketone 2: To a suspension of diazoketone 1 (26.8 g, 67 mmol) in ether/THF (750 mL, 3/2) at 0°C was added 4M HCl in dioxane (16.9 mL, 67 mmol). The solution was stirred at 0°C for 2 hr. The reaction solvent was evaporated under reduced pressure to give the chloroketone (27.7 g, 97%) as a solid.

Example A27

Chloroalcohol 3: To a solution of chloroketone 2 (127.1 g, 67 mmol) in THF (350 mL) was added water (40 mL) and the solution was cooled to 3-4°C (internal temperature). $NaBH_4$ (6.3 g, 168 mmol) was added in portions. The mixture was stirred for 1h at 0°C and the solvents were removed. The mixture was diluted with ethyl acetate and saturated $KHSO_4$ was slowly added until the pH<4 followed by saturated NaCl. The organic phase was washed with saturated NaCl, dried ($MgSO_4$) filtered and evaporated under reduced pressure. The crude product consisted of a 70:30 mixture of diastereomers by HPLC analysis (mobile phase, 77:25-CH_3CN:H_2O; flow rate: 1 mL/min; detection: 254 nm; sample volume: 20 μL; column: 5μ C18, 4.6X250 mm, Varian; retention times: major diastereomer 3, 5.4 min, minor diastereomer 4, 6.1 min). The residue was recrystallized from EtOAc/hexane twice to afford the chloro alcohol 3 (12.2g, >96% diastereomeric purity by HPLC analysis) as a white solid.

Example A28

Epoxide 5: To a solution of chloroalcohol 3 (12.17 g, 130 mmol) in EtOH (300 mL) was added KOH/EtOH solution (0.71N, 51 mL, 36 mmol). The mixture was stirred for at room temperature for 1.5h. The reaction mixture was evaporated under reduced pressure. The residue

was partitioned between EtOAc and water and the organic phase was washed with saturated NH_4Cl, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to afford the epoxide (10.8 g, 97%) as a white solid.

Example A29

Sulfonamide 6: To a suspension of epoxide 5 (10.8 g, 30 mmol) in 2-propanol (100 mL) was added isobutylamine (129.8 mL, 300 mmol) and the solution was refluxed for 1 hr. The solution was evaporated under reduced pressure to give a crude solid. The solid (42 mmol) was dissolved in CH_2Cl_2 (200 mL) and cooled to 0°C. Triethylamine (11.7 mL, 84 mmol) was added followed by the addition of 4-methoxybenzenesulfonyl chloride (8.68 g, 42 mmol) and the solution was stirred for 40 min at 0°C, warmed to room temperature and evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was recrystallized from EtOAc/hexane to give the sulfonamide (23.4 g, 91%) as a small white needles: mp 122-124°C (uncorrected).

Example A30

Carbamate 7: A solution of sulfonamide 6 (6.29 mg, 10.1 mmol) in CH_2Cl_2 (20 mL) was treated with trifluoroacetic acid (10 mL). The solution was stirred for 3 hr. Volatiles were evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase were washed with 0.5 N NaOH (2x), water (2x) and saturated NaCl, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was dissolved in CH_3CN (60 mL), cooled to 0°C and was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (298.5 g, 10 mmol, prepared according to Ghosh *et al.* J. Med. Chem. 1996, 39, 3278.) and N,N-dimethylaminopyridine (2.4 g, 20 mmol). After stirring for 1h at 0°C, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 5% citric acid. The organic phase was washed twice with 1% K_2CO_3, and then was washed with saturated NaCl, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (1/1 - EtOAc/hexane) affording the carbamate (5.4 g, 83%) as a solid: mp 128-129°C (MeOH, uncorrected).

Example A31

Phenol 8: A solution of carbamate 7 (5.4 g, 8.0 mmol) in EtOH (260 mL) and EtOAc (130 mL) was treated with 10% Pd/C (540 mg) and was stirred under H_2 atmosphere (balloon) for 3h. The reaction solution stirred with celite for 10 min, and passed through a pad of celite. The filtrate was evaporated under reduced pressure to afford the phenol as a solid (4.9 g) that contained residual solvent: mp 131-134°C (EtOAc/hexane, uncorrected).

Example A32

Dibenzylphosphonate 10: To a solution of dibenzylhydroxymethyl phosphonate (3.1 g, 10.6 mmol) in CH_2Cl_2 (30 mL) was treated with 2,6-lutidine (1.8 mL, 15.6 mmol) and the reaction flask was cooled to -50°C (external temperature). Trifluoromethanesulfonic anhydride (2.11 mL, 12.6 mmol) was added and the reaction mixture was stirred for 15 min and then the cooling bath was allowed to warm to 0°C over 45 min. The reaction mixture was partitioned between ether and ice-cold water. The organic phase was washed with cold 1M H_3PO_4, saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford triflate 9 (3.6 g, 80%) as an oil which was used directly without any further purification. To a solution of phenol 8 (3.61 g, 6.3 mmol) in THF (90 mL) was added Cs_2CO_3 (4.1 g, 12.6 mmol) and triflate 9 (4.1 g, 9.5 mmol) in THF (10 mL). After stirring the reaction mixture for 30 min at room temperature additional Cs_2CO_3 (6.96 g, 3 mmol) and triflate (1.26 g, 3 mmol) were added and the mixture was stirred for 3.5h. The reaction mixture was evaporated under reduced pressure and the residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was chromatographed on silica gel eluting (5% 2-propanol/CH_2Cl_2) to give the dibenzylphosphonate as an oil that solidified upon standing. The solid was dissolved in EtOAc, ether was added, and the solid was precipitated at room temperature overnight. After cooling to 0°C the solid was filtered and washed with cold ether to afford the dibenzylphosphonate (3.43 g, 64%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.66 (d, 2H), 7.31 (s, 10H), 7.08 (d, 2H), 6.94 (d, 2H), 6.76 (d, 2H), 5.59 (d, 1H), 5.15-4.89 (m, 6H), 4.15 (d, 2H), 3.94-3.62 (m, 10H), 3.13-2.69 (m, 7H), 1.78 (m, 1H), 1.70-1.44 (m, 2H), 0.89-0.82 (2d, 6H); ^{31}P NMR ($CDCl_3$) δ 18.7; MS (ESI) 853 (M+H).

Example A33

Phosphonic acid 11: A solution of dibenzylphosphonate 10 (3.43 g) was dissolved in EtOH/ EtOAc (150 mL/50 mL), treated with 10% Pd/C (350 mg) and was stirred under H_2 atmosphere (balloon) for 3 h. The reaction mixture was stirred with celite, and the catalyst was removed by filtration through celite. The filtrate was evaporated under reduced pressure and the residue was dissolved in MeOH and filtered with a 0.45 μM filter. After evaporation of the filtrate, the residue was triturated with ether and the solid was collected by filtration to afford the phosphonic acid (2.6 g, 94%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.77 (d, 2H), 7.19 (d, 2H), 7.09 (d, 2H), 6.92 (d, 2H), 5.60 (d, 1H), 4.95 (m, 1H), 4.17 (d, 2H), 3.94 (m, 1H), 3.89 (s, 3H), 3.85-3.68 (m, 5H), 3.42 (dd, 1H), 3.16-3.06 (m, 2H), 2.96-2.84 (m, 3H), 2.50 (m, 1H), 2.02 (m, 1H), 1.58 (m, 1H), 1.40 (dd, 1H), 0.94 (d, 3H), 0.89 (d, 3H); ^{31}P NMR ($CDCl_3$) δ 16.2; MS (ESI) 671 (M-H).

Example Section B

There is no Section B in this application.

Example Section C

Example C1

Diphenyl phosphonate **31**: To a solution of phosphonic acid **30** (11 g, 16.4 mmol) and phenol (11 g, 117 mmol) in pyridine (100 mL) was added 1, 3-dicyclohexylcarbodiimide (13.5 g, 65.5 mmol). The solution was stirred at room temperature for 5 min and then at 70°C for 2h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (100 mL) and filtered. The filtrate was evaporated under reduced pressure to remove pyridine. The residue was dissolved in ethyl acetate (250 mL) and acidified to pH = 4 by addition of HCl (0.5 N) at 0°C. The mixture was stirred at 0°C for 0.5 h, filtered and the organic phase was separated and washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified on silica gel to give diphenyl phosphonate **31** (9 g, 67%) as a solid. ^{31}P NMR ($CDCl_3$) d 12.5.

Example C2

Monophenyl phosphonate **32**: To a solution of diphenylphosphonate **31** (9.0 g, 10.9 mmol) in acetonitrile (400 mL) was added NaOH (1N, 27 mL) at 0°C. The reaction mixture was stirred at 0°C for 1 h, and then treated with Dowex (50WX8-200, 12 g). The mixture was stirred for 0.5 h at 0°C, and then filtered. The filtrate was concentrated under reduced pressure and co-evaporated with toluene. The residue was dissolved in ethyl acetate and hexane was added to precipitate out the monophenyl phosphonate **32** (8.1 g, 100%). ^{31}P NMR ($CDCl_3$) d 18.3.

Example C3

Monoamidate **33a** (R_1 = Me, R_2 = n-Bu): To a flask charged with monophenyl phosphonate **32** (4.0 g, 5.35 mmol) , was added L-alanine n-butyl ester hydrochloride (4.0 g, 22 mmol), 1, 3-dicyclohexylcarbodiimide (6.6 g, 32 mmol), and finally pyridine (30 mL) under nitrogen. The resultant mixture was stirred at 60 – 70°C for 1 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and HCl (0.2 N) and the organic layer was separated. The ethyl acetate phase was washed with water, saturated $NaHCO_3$, dried over MgSO4 , filtered and concentrated under reduced pressure. The residue was purified on silica gel (pre-treated with 10% MeOH / CH_3CO_2Et, eluting with 40%

CH_2Cl_2 / CH_3CO_2Et and CH_3CO_2Et) to give two isomers of **33a** in a total yield of 51%. Isomer A (1.1 g): 1H NMR (CDCl3) d 0.88 (m, 9H), 1.3 (m, 2H), 1.35 (d, J = 7 Hz, 3H), 1.55 (m, 2H), 1.55-1.7 (m, 2H), 1.8 (m, 1H), 2.7-3.2 (m, 7H), 3.65-4.1 (m, 9H), 3.85 (s, 3H), 4.2 (m, 1H), 4.3 (d, J = 9.6 Hz, 2H), 5.0 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.0 (d, J = 8.7 Hz, 2H), 7.1-7.3 (m, 7H), 7.7 (d, J = 8.7 Hz, 2H); ^{31}P NMR ($CDCl_3$) d 20.5. Isomer B (1.3 g) 1H NMR (CDCl3) d 0.88 (m, 9H), 1.3 (m, 2H), 1.35 (d, J = 7 Hz, 3H), 1.55 (m, 2H), 1.55-1.7 (m, 2H), 1.8 (m, 1H), 2.7-3.2 (m, 7H), 3.65-4.1 (m, 9H), 3.85 (s, 3H), 4.2-4.35 (m, 3H), 5.0 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.0 (d, J = 8.7 Hz, 2H), 7.1-7.3 (m, 7H), 7.7 (d, J = 8.7 Hz, 2H); ^{31}P NMR ($CDCl_3$) d 19.4.

Example C4

Monoamidate **33b** (R_1 = Me, R_2 = i-Pr) was synthesized in the same manner as **33a** in 77% yield. Isomer A : 1H NMR (CDCl3) d 0.9 (2d, J = 6.3Hz, 6H), 1.2 (d, J = 7 Hz, 6H), 1.38 (d, J = 7 Hz, 3H), 1.55-1.9 (m, 3H), 2.7-3.2 (m, 7H), 3.65-4.1 (m, 8H), 3.85 (s, 3H), 4.2 (m, 1H), 4.3 (d, J = 9.6 Hz, 2H), 5.0 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.0 (d, J = 8.7 Hz, 2H), 7.1-7.3 (m, 7H), 7.7 (d, J = 8.7 Hz, 2H); ^{31}P NMR ($CDCl_3$) d 20.4. Isomer B: 1H NMR (CDCl3) d 0.9 (2d, J = 6.3Hz, 6H), 1.2 (d, J = 7 Hz, 6H), 1.38 (d, J = 7 Hz, 3H), 1.55-1.9 (m, 3H), 2.7-3.2 (m, 7H), 3.65-4.1 (m, 8H), 3.85 (s, 3H), 4.2 (m, 1H), 4.3 (d, J = 9.6 Hz, 2H), 5.0 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.0 (d, J = 8.7 Hz, 2H), 7.1-7.3 (m, 7H), 7.7 (d, J = 8.7 Hz, 2H); ^{31}P NMR ($CDCl_3$) d 19.5.

Example Section D

Example D1

Cyclic Anhydride 1 (6.57 g, 51.3 mmol) was treated according to the procedure of Brown *et al., J. Amer. Chem. Soc.* 1955, 77, 1089 -1091 to afford amino alcohol 3 (2.00g, 33%). For intermediate 2 : ^{1}H NMR (CD_3OD) δ 2.40 (S, 2H), 1.20 (s, 6H).

Example D2

Amino alcohol 3 (2.0 g, 17 mmol) was stirred in 30 mL 1:1 THF: water. Sodium Bicarbonate (7.2 g, 86 mmol) was added, followed by Boc Anhydride (4.1 g, 19 mmol). The reaction was stirred for 1 hour, at which time TLC in 5% methanol/DCM with ninhydrin stain showed completion. The reaction was partitioned between water and ethyl acetate. The organic layer was dried and concentrated, and the resulting mixture was chromatographed on silica in 1:1 hexane: ethyl acetate to afford two fractions, "upper" and "lower" each having the correct mass. By NMR the correct product 4 was "lower" (0.56 g, 14%) ^{1}H NMR ($CDCl_3$) δ 3.7 (t, 2H), 3.0 (d,2H), 1.45 (t, 2H) 1.4 (s, 9H), 0.85 (s, 6H), MS (ESI): 240 (M + 23).

Example D3

Sodium Hydride (60% emulsion in oil) was added to a solution of the alcohol 4 (1.1g, 5.2 mmol) in dry DMF in a 3-neck flask under dry nitrogen. Shortly afterward triflate 35 (2.4 g, 5.7 mmol) was added with stirring for 1.5 hrs. Mass spectrometry showed the presence of the starting material (240, M+23), thus 100 mg more 60% sodium hydride emulsion as well as ~1 g more triflate were added with an additional hour of stirring. The reaction was quenched by the addition of saturated $NaHCO_3$ then partitioned between ethyl acetate and water. The organic layer was dried with brine and $MgSO_4$ and eluted on silica with 1:1 hexane:ethyl acetate to afford 5 (0.445 g, 15%). NMR showed some contamination with alcohol 4 starting material. ^{1}H NMR ($CDCl_3$): δ 7.28 (s, 10H), 5.00 (m, 4H), 3.70 (t, 2H), 2.94, (d, 2H), 1.44 (t, 2H), 1.40 (s, 9H), 0.83 (s, 6H) MS (ESI): 514 (M+23).

Example D4

Phosphonate ester 5 (0.445 g, 0.906 mmol) was stirred with with 20% TFA in DCM. (5 mL) TLC showed completion in 1 hr time. The reaction was azeotroped with toluene then run

on a silica gel column with 10% methanol in DCM. Subsequently, the product was dissolved in ethyl acetate and shaken with saturated sodium bicarbonate: water (1:1), dried with brine and magnesium sulfate to afford the free amine 6 (30mg, 8.5%). ^{1}H NMR ($CDCl_3$): δ 7.30 (s, 10H), 5.00 (m, 4H), 3.67 (d, 2H), 3.47, (t, 2H), 2.4-2.6 (brs) 1.45 (t, 2H), 0.82 (s, 6H), MS (ESI): 393 (M+1).

Example D5

Amine 6 (30 mg, 0.08 mmol) and epoxide 7 (21 mg, 0.08 mmol) were dissolved in 2 mL IprOH and heated to reflux for 1 hr then monitored by TLC in 10% MeOH/DCM. Added ~20 mg more epoxide 7 and continued reflux for 1 hr. Cool to room temperature, dilute with ethyl acetate, shake with water and brine, dry with magnesium sulfate. Silica gel chromatography using first 5% then 10% MeOH in EtOAc yielded amine 8 (18 mg, 36%). ^{1}H NMR ($CDCl_3$): δ 7.30 (s, 10H), 7.20-7-14 (m, 5H), 5.25-4.91 (m, 4H), 3.83, (m, 1H), 3.71 (d, 2H) 3.64 (m, 1H), 3.54 (t, 2H), 3.02-2.61 (m, 5H), 2.65-2.36 (dd, 2H) (t, 2H), 1.30 (s, 9H) 0.93 (s, 9H) 0.83 (t, 2H) MS (ESI) 655 (M+1).

Example D6

Amine 8 (18 mg, 0.027 mmol) was dissolved in 1 mL DCM then acid chloride 9 (6 mg, 0.2 mmol) followed by triethylamine (0.004 mL, 0.029 mmol). The reaction was monitored by TLC. Upon completion the reaction was diluted with DCM shaken with 5% citric acid, saturated sodium bicarbonate, brine, and dried with $MgSO_4$. Purification on silica (1:1 Hexane:EtOAc) afforded sulfonamide 10 (10.5 mg, 46%). ^{1}H NMR ($CDCl_3$): δ 7.69 (d, 2H), 7.30 (s, 10H), 7.24-7-18 (m, 5H), 5.00 (m, 4H), 4.73, (d, 1H), 4.19 (s, 1H) 3.81 (m, 1H), 3.80 (s, 3H), 3.71 (d,2H), 3.57 (t, 2H), 3.11-2.95 (m, 5H) 2.75 (m,1H)1.25 (s, 1H), 0.90 (s, 6H) MS (ESI) 847 ($M+Na^{+}$).

Example D7

Sulfonamide 10 (10.5 mg, 0.013 mmol) was stirred at room temperature in 20% TFA/DCM. Once Boc deprotection was complete by TLC (1:1 Hexane:EtOAc) and MS, the reaction was azeotroped with toluene. The TFA salt of the amine was dissolved in acetonitrile (0.5 mg) and to this were added carbonate 11 (4.3 mg, 0.014 mmol) followed by DMAP (4.6 mg, 0.038 mg). Stir at room temp until TLC (1:1 Hexane:EtOAc) shows completion. Solvent was evaporated and the residue was redissolved in EtOAc then shaken with saturated $NaHCO_3$. The

organic layer was washed with water and brine, then dried with $MgSO_4$ Purification on silica with Hexane: EtOAc afforded compound 12 (7.1 mg, 50%). ^1H NMR ($CDCl_3$): δ 7.75 (d, 2H) 7.24-7.35 (15H) 6.98 (d, 2H), 5.62 (d, 1H) 5.04 (m, 4H) 4.98 (m, 1H) 4.03 (m, 1H), 3.85 (s, 3H), 3.61-3.91 (9H), 3.23-3.04 (5H) 2.85 (m, 1H), 2.74 (m,1H) 1.61 (d, 2H), 1.55 (m, 1H) 1.36 (m, 1H) 0.96 (d, 6H) MS (ESI): 903 (M+23).

Example D8

Compound 12 (6.1 mg, 0.007 mmol) was dissolved in 1 mL 3:1 EtOH:EtoAc. Palladium catalyst (10% on C, 1mg) was added and the mixture was purged three times to vacuum with 1 atmosphere hydrogen gas using a balloon. The reaction was stirred for 2 hrs, when MS and TLC showed completion. The reaction was filtered through Celite with EtOH washing and all solvent to was evaporated to afford final compound 13 (5mg, 100%). ^1H NMR (CD_3OD): δ 7.79 (d, 2H) 7.16-7.24 (5H) 7.09 (d, 2H) 5.58 (d, 1H) 4.92 (m, 1H) 3.97 (m, 1H), 3.92 (dd,1H) 3.89 (s, 3H) 3.66-3.78 (8H) 3.40 (d,1H), 3.37 (dd, 1H), 3.15 (m, 1H) 3.12 (dd,1H) 2.96 (d, 1H), 2.87 (m, 1H), 2.74 (m,1H) 2.53 (m, 1H) 1.70 (m, 2H), 1.53 (m, 1H) 1.32 (m, 1H) 1.04 (d, 6H) MS (ESI): 723 (M+23).

Example D9

Amino Alcohol 14 (2.67g, 25.9 mmol) was dissolved in THF with stirring and Boc Anhydride (6.78g, 31.1 mmol) was added. Heat and gas evolution ensued. TEA (3.97 mL, 28.5 mmol) was added and the reaction was stirred overnight. In the morning, the reaction was quenched by the addition of saturated $NaHCO_3$. The organic layer was separated out and shaken with water, dried with brine and $MgSO_4$ to afford 15 which was used without further purification. (100% yield) (some contamination): ^1H NMR ($CDCl_3$): δ 3.76 (t ,1H) 3.20, (d,2H), 2.97 (d, 2H), 1.44 (s, 9H), 0.85 (s, 6H).

Example D10

A solution of the alcohol 15 (500 mg, 2.45 mmol) in dry THF was cooled under dry N_2 with stirring. To this was added n-butyl lithium (1.29 mL, 2.71 mmol) as a solution in hexane in a manner similar to that described in Tetrahedron. 1995, 51 #35, 9737-9746. Triflate 35 (1.15 g, 2.71 mmol) was added neat with a tared syringe. The reaction was stirred for four hours, then quenched with saturated $NaHCO_3$. The mixture was then partitioned between water and EtOAc.

The organic layer was dried with brine and $MgSO_4$, then chromatographed on silica in 1:1 Hexane:EtOAc to afford phosphonate 16 (445mg, 38%) ^{1}H NMR ($CDCl_3$): δ 7.37 (m, 10H), 5.09 (m, 4H), 3.73-3.75 (m, 2H), 3.24 (s,2H), 3.02 (d, 2H), 1.43 (s, 9H), 0.86 (s, 6H).

Example D11

Phosphonate 16 (249 mg, 0.522 mmol) was stirred in 20% TFA/DCM for 1 hr. The reaction was then azeotroped with toluene. The residue was re-dissolved in EtOAc, then shaken with water: saturated $NaHCO_3$ (1:1). The organic layer was dried with brine and $MgSO_4$ and solvent was removed to afford amine 17 (143 mg, 73%) ^{1}H NMR ($CDCl_3$): δ 7.30 (s, 10H), 5.05-4.99 (m, 4H), 3.73 (d, 2H), 3.23 (s, 2H), 2.46 (brs, 2H), 0.80 (s, 6H) ^{31}P NMR ($CDCl_3$): δ 23.77 (s).

Example D12

Amine 17 (143 mg, 0.379 mmol) and epoxide 7 (95 mg, 0.360 mmol) were dissolved in 3 mL IprOH and heated to 85°C for 1 hr. The reaction was cooled to room temperature overnight then heated to 85°C for 1 hr more in the morning. The reaction was then diluted with EtOAc, shaken with water, dried with brine $MgSO_4$ and concentrated. The residue was eluted on silica in a gradient from 5% to 10% MeOH in DCM to afford compound 18 (33 mg, 14%).

Example D13

Mix compound 18 (33 mg, 0.051 mmol) and chlorosulfonyl compound 9 (11 mg, 0.054 mmol) in 2 mL DCM then add TEA (0.0075 mL, 0.054 mmol), stir for 5 hrs. TLC in 1:1 EtOAc: hexane shows reaction not complete. Place in freezer overnight. In the morning, take out of freezer, stir for 2 hrs, TLC shows completion. Workup done with 5% citric acid, saturated $NaHCO_3$, then dry with brine and $MgSO_4$. The reaction mixture was concentrated and chromatographed on a Monster Pipette column in 1:1 hexane: EtOAc then 7:3 hexane: EtOAc to avail compound 19 (28 mg , 67%) ^{1}H NMR ($CDCl_3$): δ 7.37 (d, 2H), 7.20 (m, 15H), 6.90 (d, 2H), 5.07-4.93 (m, 4H), 4.16 (brs, 1H), 3.80 (s, 3H), 3.75-3.37 (m, 4H), 3.36 (d, 1H), 3.20-2.93 (m, 6H), 2.80- 2.75 (dd, 1H).

Example D14

Compound 19 (28 mg, 0.35 mmol) was stirred in 4 mL DCM with addition of 1 mL TFA. Stir for 45 minutes, at which time complete deprotection was noted by TLC as well as MS.

Azeotrope with toluene. The residue was dissolved in 1 mL CH_3CN, cooled to 0°C. Bis-Furan *para*-Nitro phenol carbonate 11 (12 mg, 0.038 mmol), dimethyl amino pyridine (~ 1 mg, 0.008 mmol) and diisopropylethylamine (0.018 mL, 0.103 mmol) were added. The mixture was stirred and allowed to come to room temperature and stirred until TLC in 1:1 hexane:EtOAc showed completion. The reaction mixture was concentrated and the residue was partitioned between saturated $NaHCO_3$ and EtOAc. The organic layer was dried with brine and $MgSO_4$, then chromatographed on silica with hexane:EtOAc to afford compound 20 (20 mg, 67%). ^{1}NMR ($CDCl_3$): δ 7.76 (d, 2H), 7.34–7.16 (m, 15 H), 7.07 (d, 2H), 5.56 (d, 1H), 5.09 (m, 4H), 4.87 (m, 1H), 4.01 (m, 1H), 3.91 (m, 2H), 3.87 (s, 3H), 3.86 (m, 1H), 3.69 (m, 1H), 3.67 (m, 1H) 3.60 (d, 2H) 3.28 (m, 1H) 3.25 (d, 2H), 3.32 (d, 1H), 3.13 (m, 1H), 3.02 (m, 1H) 2.85 (d, 1H), 2.83 (m, 1H) 2.52 (m, 1H) 1.47 (m, 1H), 1.31 (m, 1H) 0.98 (s, 3H), 0.95 (s,3H).

Example D15

Compound 20 (7 mg, 0.008 mmol) was treated in a manner identical to example 8 to afford compound 21 (5 mg, 90%) ^{1}H NMR ($CDCl_3$): δ 7.80 (d, 2H), 7.25–7.16 (m, 5H), 7.09 (d, 2H), 5.58 (d, 1H), 4.92 (m, 1H), 3.99 (m, 1H), 3.92 (m, 1H), 3.88 (s, 3H), 3.86 (m, 1H), 3.77 (m, 1H), 3.75 (m, 1H), 3.73 (m, 1H), 3.71 (m, 1H) 3.71 (m, 1H), 3.68 (m, 1H), 3.57 (d,1H), 3.41 (d, 1H), 3.36 (m, 1H), 3.29 (d, 1H), 3.25 (d, 2H), 3.18 (m, 1H), 3.12 (m, 1H), 3.01 (d, 1H) 2.86 (m, 1H), 2.53 (m, 1H) 1.50 (m, 1H), 1.33 (m, 1H), 1.02 (s, 3H), 0.99 (s, 3H).

Example D16

Compound 15 (1.86 g, 9.20 mmol) was treated with triflate 22 in a manner identical to example 10 to afford compound 23 (0.71 g, 21.8%) ^{1}H NMR ($CDCl_3$): δ 5.21 (brs, 1H) 4.16-4.07 (m, 4H), 3.71-3.69 (d, 2H), 3.24 (s, 2H), 1.43 (s, 9H), 1.34-1.28 (m, 6H) 0.86 (s, 6H).

Example D17

Compound 23 (151 mg, 0.427 mmol) was dissolved in 10 mL DCM and 1.0 mL TFA was added. The reaction was stirred until completion. The reaction was azeotroped with toluene and the residue was then dissolved in THF and treated with basic Dowex resin beads. Afterwards, the beads were filtered away and solvent was removed to avail compound 24 (100 mg, 92%) ^{1}H NMR ($CDCl_3$): δ 4.15-4.05 (m, 4H), 3.72-3.69 (d, 2H), 3.27 (s, 2H), 1.30-1.26 (m, 6H) 0.81 (s, 6H).

Example D18

Compound 24 (100 mg, 0.395 mmol) was treated in a manner identical to example 12 to avail compound 25 (123 mg, 60%). ^{1}H NMR ($CDCl_3$): δ 7.26–7.13 (m, 5H), 4.48-4.83 (d, 1H) 4.17-4.06 (m, 4H), 3.75 (d, 2H) 3.56 (brs, 1H), 3.33 (s, 2H), 2.93-2.69 (m, 4H), 2.44-2.55 (dd, 2H) 1.32 (m, 6H), 0.916 (s, 6H).

Example D19

Compound 25 (88 mg, 0.171 mmol) was treated in a manner identical to example 13 to afford compound 26 (65 mg, 55%) ^{1}H NMR ($CDCl_3$): δ 7.26–7.13 (m, 5H), 4.48-4.83 (d, 1H) 4.17-4.06 (m, 4H), 3.75 (d, 2H) 3.56 (brs, 1H), 3.33 (s, 2H), 2.93-2.69 (m, 4H), 2.44-2.55 (dd, 2H) 1.32 (m, 6H), 0.916 (s, 6H).

Example D20

Compound 26 (65 mg, 0.171 mmol) was treated in a manner identical to example 14 to afford compound 27 (49 mg, 70%) ^{1}H NMR:
($CDCl_3$):δ 7.75 (d, 2H), 7.25–7.24 (m,4 H), 7.18 (m, 1H) 6.99 (d, 2H), 5.63 (d, 1H), 5.01 (m, 1H), 4.16 (m, 4H), 3.94 (m, 1H), 3.88 (m, 1H), 3.88 (s, 3H), 3.84 (m, 1H), 3.81 (m, 1H), 3.74 (m, 2H),), 3.70 (m, 1H), 3.69 (m, 1H) 3.43 (m, 1H), 3.24 (m, 1H), 3.22 (m, 2H) 3.21 (m, 2H) 3.12 (m, 1H), 3.02 (m, 1H) 2.86 (m, 1H), 2.72 (m, 1H), 1.54 (m, 1H), 1.38 (m, 1H) 1.35 (m, 6H) 1.00 (s, 3H), 0.96 (s,3H).

Example D21

Boc protected amine 28 (103 mg, 0.153 mmol) was dissolved in DCM (5 mL). The stirred solution was cooled to 0°C. BBr_3 as a 1.0 M solution in DCM (0.92 mL, 0.92 mmol) was added dropwise over 10 min, and the reaction was allowed to continue stirring at 0°C for 20 min. The reaction was warmed to room temperature and stirring was continued for 2 hours. The reaction was then cooled to 0°C and quenched by dropwise addition of MeOH (1 mL). The reaction mixture was evaporated and the residue suspended in methanol which was removed under reduced pressure. The procedure was repeated for EtOAc and finally toluene to afford free amine HBr salt 29 (107 mg, >100%) which was used without further purification.

Example D22

Amine HBr salt 29 (50 mg, 0.102 mmol) was suspended in 2 mL CH_3CN with stirring then cooled to 0°C. DMAP (25 mg, 0.205 mmol) was added, followed by Carbonate11. The reaction was stirred at 0°C for 1.5 hrs then allowed to warm to room temperature. The reaction was stirred overnight. A few drops Acetic acid were added to the reaction mixture, which was concentrated and re-diluted with ethyl acetate, shaken with 10% citric acid then saturated $NaHCO_3$. The organic layer was dried with brine and $MgSO_4$ and eluted on silica to afford di-phenol 30 (16 mg, 28%) ^{1}H NMR (CD_3OD): δ 7.61, (d, 2H), 7.01 (d, 2H), 6.87 (d, 2H), 6.62 (d, 2H), 5.55 (d, 1H), 4.93 (m, 1H), 3.92 (m, 2H), 3.79 (m, 5H), 3.35 (m, 1H), 3.07 (m, 2H), 2.88 (m, 3H), 2.41 (m, 1H), 2.00 (m, 1H), 1.54 (m, 1H), 1.31 (dd, 1H) 0.89-0.82 (dd, 6H).

Example D23

A solution of di-phenol 30 (100 mg, 0.177 mmol) was made in CH_3CN that had been dried over K_2CO_3. To this, the triflate (0.084 mL, 0.23 mmol) was added, followed by Cs_2CO_3 (173 mg, 0.531 mmol). The reaction was stirred for 1 hr. TLC (5% IprOH/DCM) showed 2 spots with no starting materials left. Solvent was evaporated and the residue was partitioned between EtOAc and water. The organic layer was washed with saturated $NaHCO_3$, then dried with brine and $MgSO_4$. The mixture was separated by column chromatography on silica with 3% IprOH in DCM. The upper spot 31 (90 mg, 46%) was confirmed to be the *bis* alkylation product. The lower spot required further purification on silica gel plates to afford a single *mono* alkylation product 32 (37 mg, 26%). The other possible alkylation product was not observed. NMR : ^{1}H NMR ($CDCl_3$): *for 31:* δ 7.57 (d, 2H), 7.37 (m, 10H) 7.03 (d, 2H), 6.99 (d, 2H), 6.73 (d, 2H), 5.69 (d, 1H), 5.15-5.09 (m, 4H), 5.10 (m, 1H), 4.32 (d, 2H), 4.02 (d, 1H), 3.82 (m, 1H) 3.81 (m, 1H), 3.93-3.81 (m, 2H), 3.74 (d, 1H), 3.06 (m, 1H), 3.00 (m, 1H), 2.96 (m, 1H), 2.91 (m, 1H) 2.77 (m, 1H) 2.64 (m, 1H) 2.47 (m, 1H) 1.82 (m, 2H) 1.79 (m, 1H), 0.94-0.86 (dd, 6H) *for 32:* δ 7.68 (d, 2H), 7.33-7.35 (m, 20H), 7.11 (d, 2H), 6.96 (d, 2H), 6.80 (d, 2H), 5.26 (d, 1H), 5.11(m, 8H), 5.00 (m, 1H) 4.23 (d, 2H), 4.19 (d, 2H), 3.93 (m, 1H), 3.82-3.83 (m, 3H), 3.68-3.69 (m, 2H) 3.12-2.75 (m, 7H), 1.82 (m, 1H), 1.62-1.52 (d, 2H), 0.89-0.86 (dd, 6H).

Example D24

Ref: *J. Med. Chem.* 1992, 35 10,1681-1701.

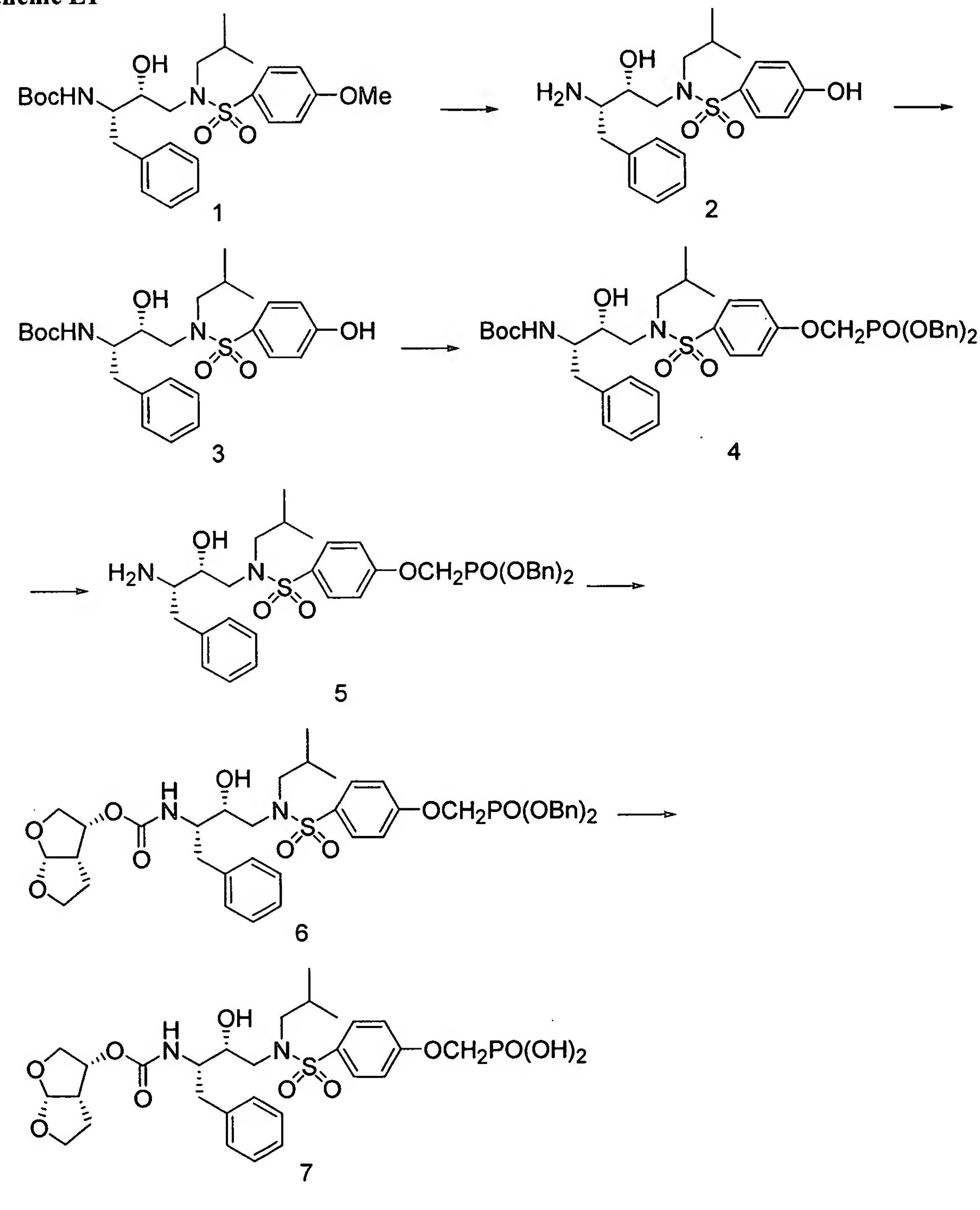
To a solution of phosphonate 32 (100 mg, 0.119 mmol) in dry dioxane was added Cs_2CO_3 (233 mg, 0.715 mmol), followed by 2-(dimethylamino) ethyl chloride hydrochloride salt (69 mg, 0.48 mmol). The reaction was stirred at room temperature and monitored by TLC. When it was determined that starting material remained, additional Cs_2CO_3 (233 mg, 0.715 mmol) as well as amine salt (69 mg, 0.48 mmol) were added and the reaction was stirred overnight at 60°C. In the morning when TLC showed completion the reaction was cooled to room temperature, filtered, and concentrated. The product amine 33 (40 mg, 37%) was purified on silica. Decomposition was noted as lower spots were seen to emerge with time using 15% MeOH in DCM on silica.

Example D25

Amine 33 (19 mg, 0.021 mmol) was dissolved in 1.5 mL DCM. This solution was stirred in an icebath. Methane sulfonic acid (0.0015 mL, 0.023 mmol) was added and the reaction was stirred for 20 minutes. The reaction was warmed to room temperature and stirred for 1 hour. The product, amine mesylate salt 34 (20 mg, 95%) was precipitated out by addition of hexane. ^{1}H NMR (CD_3OD): δ 7.69 (d, 2H), 7.35 (m, 10H), 7.15 (m, 4H) 6.85 (m, 2H), 5.49 (d, 1H), 5.10 (m, 4H), 4.83 (m, 1H), 4.62 (d, 2H), 4.22 (m, 2H), 3.82 (m, 1H), 3.56 (m, 1H), 3.48 (m, 2H), 3.35 (m, 1H), 2.99 (m, 1H), 2.95 (m, 1H), 2.84 (s, 6H), 2.78 (m, 1H), 2.75 (m, 1H), 2.70 (m, 1H), 2.40 (m, 1H) 1.94 (m, 1H), 1,43 (m, 1H), 1.27 (m, 1H), 0.77 (dd, 6H).

Example Section E

Scheme E1

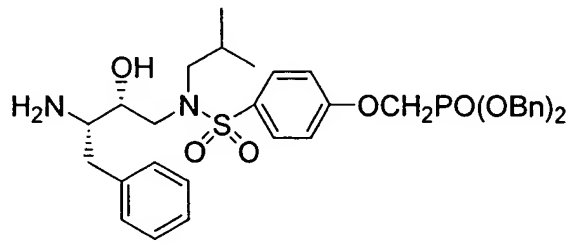


Example E1

To a solution of phenol **3** (336 mg, 0.68 mmol) in THF (10 mL) was added Cs_2CO_3 (717 mg, 2.2 mmol) and triflate (636 mg, 1.5 mmol) in THF (3 mL). After the reaction mixture was

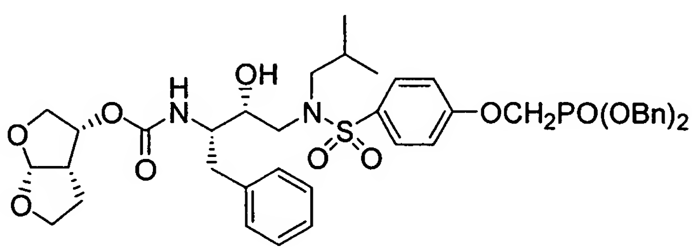
stirred for 30 min at room temperature, the mixture was partitioned between EtOAc and water. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 40-50% EtOAc/hexane) to give dibenzylphosphonate **4** (420 mg, 80%) as a colorless oil.

Example E2



To a solution of dibenzylphosphonate **4** (420 mg, 0.548 mmol) in CH_2Cl_2 (10 mL) was added TFA (0.21 mL, 2.74 mmol). After the reaction mixture was stirred for 2 h at room temperature, additional TFA (0.84 mL, 11 mmol) was added and the mixture was stirred for 3 h. The reaction mixture was evaporated under reduced pressure and the residue was partitioned between EtOAc and 1M $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give amine **5** (325 mg, 89%).

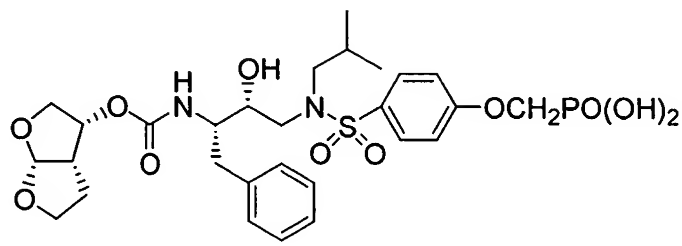
Example E3



To a solution of carbonate (79 mg, 0.27 mmol), amine **5** (178 mg, 0.27 mmol), and CH_3CN (10 mL) was added DMAP (66 mg, 0.54 mmol) at 0°C. After the reaction mixture was warmed to room temperature and stirred for 16 hours, the mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel (eluting 60-90% EtOAc/hexane) to give a mixture of carbamate **6** and starting carbonate. The mixture was further purified by HPLC on C18 reverse phase chromatography (eluting 60% CH_3CN/water) to give carbamate **6** (49 mg, 22%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, 2H), 7.22

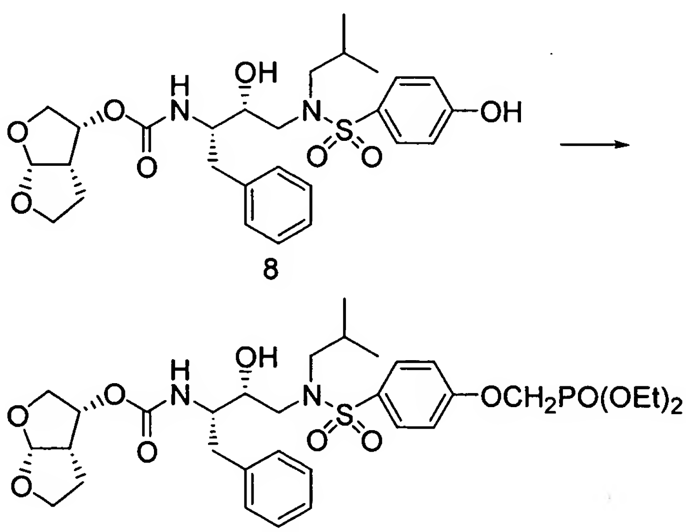
(m, 15 H), 6.95 (d, 2H), 5.62 (d, 1H), 5.15 (dt, 4H), 5.00 (m, 2H), 4.21 (d, 2H), 3.88 (m, 4H), 3.67 (m, 3H), 3.15 (m, 2H), 2.98 (m, 3H), 2.80 (m, 2H), 1.82 (m, 1H), 1.61 (m, 1H), 0.93 (d, 3H), 0.88 (d, 3H).

Example E4



To a solution of carbamate **6** (21 mg, 0.026 mmol) in EtOH / EtOAc (2 mL/1 mL) was added 10% Pd/C (11 mg). After the reaction mixture was stirred under H_2 atmosphere (balloon) for 2 hours, the mixture was filtered through Celite. The filtrate was evaporated under reduced pressure to give phosphonic acid **7** (17 mg, 100%) as a colorless solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.73 (d, 2H), 7.19 (m, 5H), 7.13 (d, 2H), 5.53 (d, 1H), 4.26 (d, 2H), 3.86 (m, 1H), 3.64 (m, 5H), 3.38 (d, 1H), 3.13 (d, 1H), 3.03 (dd, 1H), 2.86 (m, 3H), 2.48 (m, 1H), 1.97 (m, 1H), 1.47 (m, 1H), 1.28 (m, 2H), 1.13 (t, 1H), 0.88 (d, 3H), 0.83 (d, 3H).

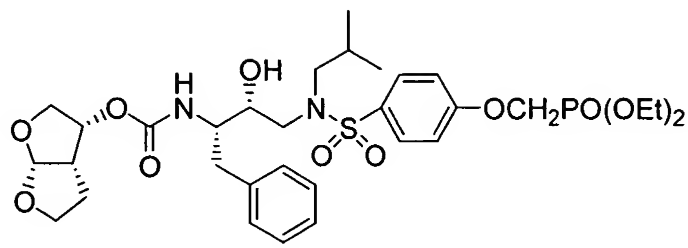
Scheme E2



8

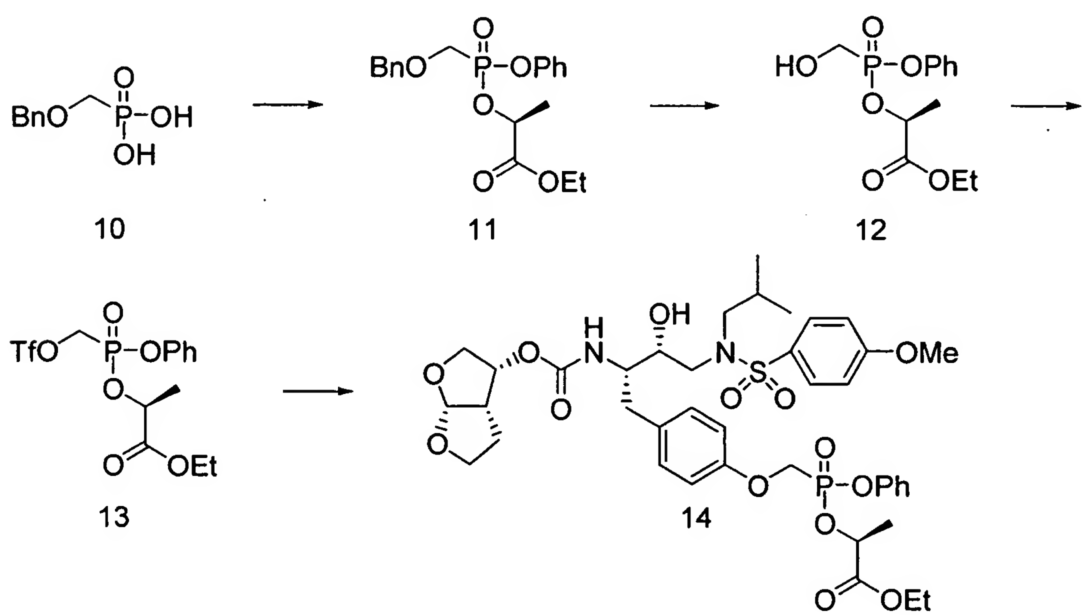
9

Example E5

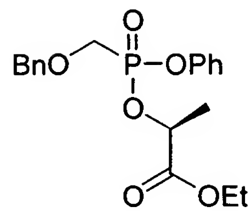


To a solution of phenol **8** (20 mg, 0.036 mmol) and triflate (22 mg, 0.073 mmol) in THF (2 mL) was added Cs_2CO_3 (29 mg, 0.090 mmol). After the reaction mixture was stirred for 30 min at room temperature, the mixture was partitioned between EtOAc and water. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by preparative thin layer chromatography (eluting 80% EtOAc/hexane) to give diethylphosphonate **9** (21 mg, 83%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, 2H), 7.25 (m, 5H), 7.07 (d, 2H), 5.64 (d, 1H), 5.01 (m, 2H), 4.25 (m, 6H), 3.88 (m, 4H), 3.70 (m, 3H), 2.97 (m, 6H), 1.70 (m, 4H), 1.38 (t, 6H), 0.92 (d, 3H), 0.88 (d, 3H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 18.1.

Scheme E3

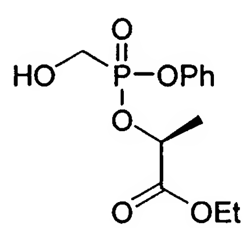


Example E6



To a solution of phosphonic acid **10** (520 mg, 2.57 mmol) in CH_3CN (5 mL) was added thionyl chloride (0.75 mL, 10.3 mmol) and heated to 70°C in an oil bath. After the reaction mixture was stirred for 2 h at 70°C, the mixture was concentrated and azeotroped with toluene. To a solution of the crude chloridate in toluene (5 mL) was added tetrazole (18 mg, 0.26 mmol) at 0°C. To this mixture was added phenol (121 mg, 1.28 mmol) and triethylamine (0.18 mL, 1.28 mmol) in toluene (3 mL) at 0°C. After the reaction mixture was warmed to room temperature and stirred for 2 h, ethyl lactate (0.29 mL, 2.57 mmol) and triethylamine (0.36 mL, 2.57 mmol) in toluene (2.5 mL) were added. The reaction mixture was stirred for 16 hours at room temperature, at which time the mixture was partitioned between EtOAc and sat. NH_4Cl. The organic phase was washed with sat. NH_4Cl, 1M $NaHCO_3$, and brine, then dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 20-40% EtOAc/hexane) to give two diastereomers of phosphonate **11** (66 mg, 109 mg, 18% total) as colorless oils.

Example E7A

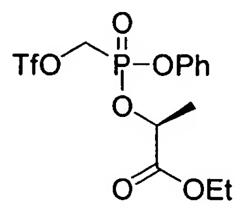


To a solution of phosphonate **11** isomer A (66 mg, 0.174 mmol) in EtOH (2 mL) was added 10% Pd/C (13 mg). After the reaction mixture was stirred under H_2 atmosphere (balloon) for 6 h, the mixture was filtered through Celite. The filtrate was evaporated under reduced pressure to give alcohol **12** isomer A (49 mg, 98%) as a colorless oil.

Example E7B

To a solution of phosphonate **11** isomer B (110 mg, 0.291 mmol) in EtOH (3 mL) was added 10% Pd/C (22 mg). After the reaction mixture was stirred under H_2 atmosphere (balloon) for 6 h, it was filtered through Celite. The filtrate was evaporated under reduced pressure to give alcohol **12** isomer B (80 mg, 95%) as a colorless oil.

Example E8A

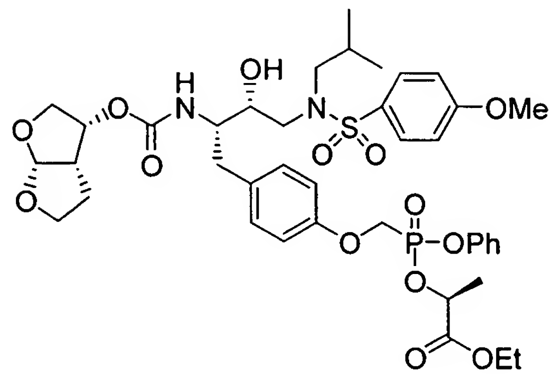


To a solution of alcohol **12** isomer A (48 mg, 0.167 mmol) in CH_2Cl_2 (2 mL) was added 2,6-lutidine (0.03 mL, 0.250 mmol) and trifluoromethanesulfonic anhydride (0.04 mL, 0.217 mmol) at -40°C (dry ice-CH_3CN bath). After the reaction mixture was stirred for 15 min at -40°C, the mixture was warmed to 0°C and partitioned between Et_2O and 1M H_3PO_4. The organic phase was washed with 1M H_3PO_4 (3 times), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give triflate **13** isomer A (70 mg, 100%) as a pale yellow oil.

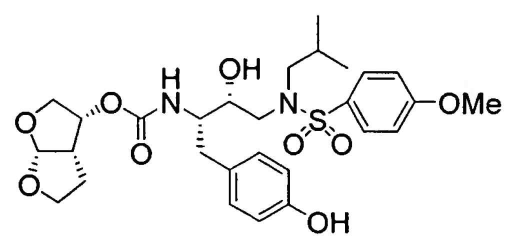
Example E8B

To a solution of alcohol **12** isomer B (80 mg, 0.278 mmol) in CH_2Cl_2 (3 mL) was added 2,6-lutidine (0.05 mL, 0.417 mmol) and trifluoromethanesulfonic anhydride (0.06 mL, 0.361 mmol) at -40°C (dry ice-CH_3CN bath). After the reaction mixture was stirred for 15 min at -40°C, the mixture was warmed to 0°C and partitioned between Et_2O and 1M H_3PO_4. The organic phase was washed with 1M H_3PO_4 (3 times), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give triflate **13** isomer B (115 mg, 98%) as a pale yellow oil.

Example E9A



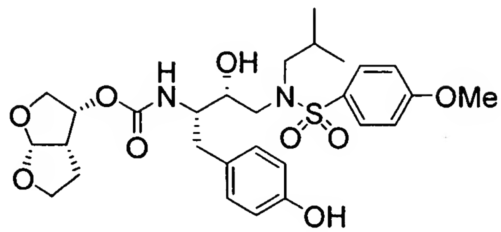
To a solution of phenol (64 mg, 0.111 mmol):



and triflate **13** isomer A (70 mg, 0.167 mmol) in THF (2 mL) was added Cs_2CO_3 (72 mg, 0.222 mmol). After the reaction mixture was stirred for 30 min at room temperature, the mixture was partitioned between EtOAc and water. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 60-80% EtOAc/hexane) to give a mixture. The mixture was further purified by HPLC on C18 reverse phase chromatography (eluting 55% CH_3CN/water) to give phosphonate **14** isomer A (30 mg, 32%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, 2H), 7.26 (m, 6H), 7.00 (m, 5H), 5.65 (d, 1H), 5.14 (m, 1H), 5.00 (m, 2H), 4.54 (dd, 1H), 4.44 (dd, 1H), 4.17 (m, 2H), 3.96 (dd, 1H), 3.86 (m, 5H), 3.72 (m, 3H), 3.14 (m, 1H), 2.97 (m, 4H), 2.79 (m, 2H), 1.83 (m, 1H), 1.62 (m, 3H), 1.50 (d, 3H), 1.25 (m, 3H), 0.93 (d, 3H), 0.88 (d, 3H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 17.4.

Example E9B

To a solution of phenol (106 mg, 0.183 mmol):



and triflate **13** isomer B (115 mg, 0.274 mmol) in THF (2 mL) was added Cs_2CO_3 (119 mg, 0.366 mmol). After the reaction mixture was stirred for 30 min at room temperature, the mixture was partitioned between EtOAc and water. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 60-80% EtOAc/hexane) to give a mixture. The mixture was further purified by HPLC on C18 reverse phase chromatography (eluting 55% CH_3CN/water) to give phosphonate **14** isomer B (28 mg, 18%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, 2H), 7.26 (m, 6H), 6.94 (m, 5H), 5.66 (d, 1H), 5.17 (m, 1H), 4.99 (m, 2H), 4.55 (m, 1H), 4.42 (m, 1H), 4.16 (m, 2H), 3.97 (m, 1H), 3.85 (m, 5H), 3.72 (m, 3H), 3.13 (m, 1H), 2.97 (m, 4H), 2.80 (m, 2H), 1.83 (m, 1H), 1.60 (m, 6H), 1.22 (m, 3H), 0.93 (d, 3H), 0.88 (d, 3H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 15.3.

Resolution of Compound 14 Diastereomers

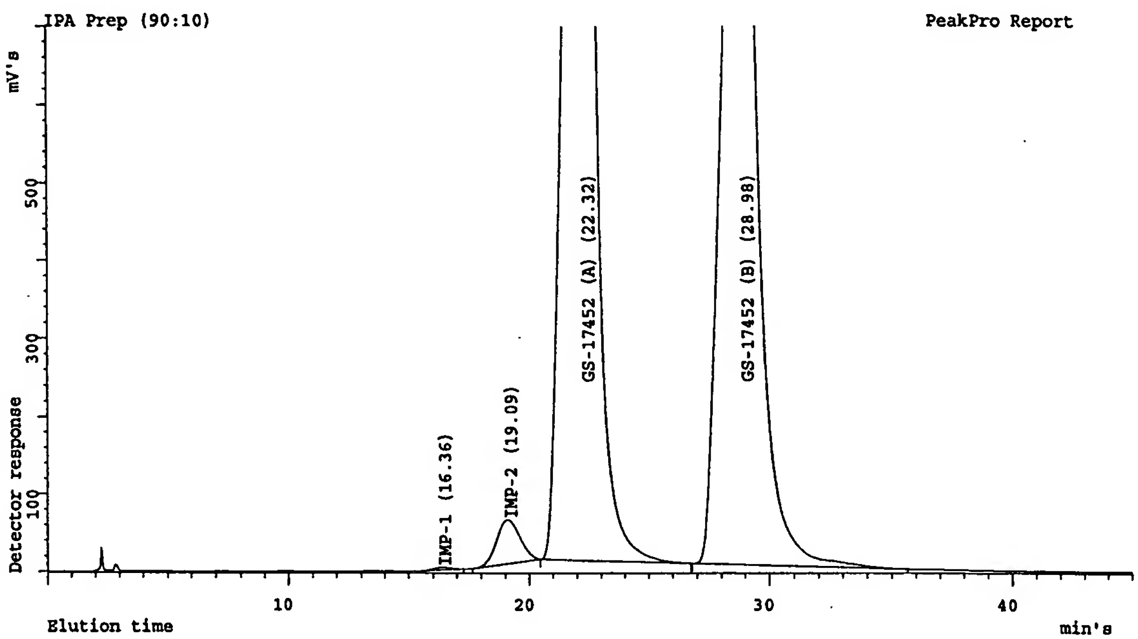
Analysis was performed on an analytical Alltech Econosil column, conditions described below, with a total of about 0.5 mg **14** injected onto the column. This lot was a mixture of major and minor diastereomers where the lactate ester carbon is a mix of R and S configurations. Up to 2 mg could be resolved on the analytical column. Larger scale injections (up to 50 mg **14**) were performed on an Alltech Econosil semi-preparative column, conditions described below.

The isolated diastereomer fractions were stripped to dryness on a rotary evaporator under house vacuum, followed by a final high vacuum strip on a vacuum pump. The chromatographic solvents were displaced by two portions of dichloromethane before the final high vacuum strip to aid in removal of trace solvents, and to yield a friable foam.

The bulk of the diastereomer resolution was performed with *n*-heptane substituted for hexanes for safety considerations.

Sample Dissolution: While a fairly polar solvent mixture is described below, the sample may be dissolved in mobile phase with a minimal quantity of ethyl alcohol added to dissolve the sample.

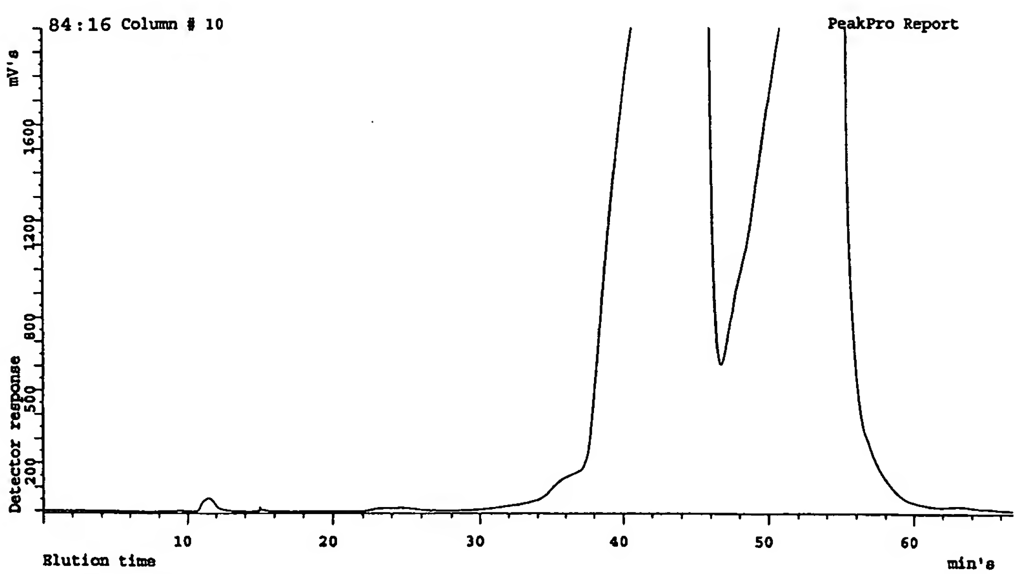
Analytical Column, 0.45 mg Injection, Hexanes – IPA (90:10)



HPLC CONDITIONS

Column	: Alltech Econosil, 5 µm, 4.6 x 250 mm
Mobile Phase	: Hexanes – Isopropyl Alcohol (90:10)
Flow Rate	: 1.5 mL/min
Run Time	: 50 min
Detection	: UV at 242 nm
Temperature	: Ambient
Injection Size	: 100 µL
Sample Prep.	: ~ 5 mg/mL, dissolved in hexanes – ethyl alcohol (75:25)
Retention Times	: **14** ~ 22 min
	: **14** ~ 29 min
	: Less Polar Impurity ~ 19 min

Semi-Preparative Column, 50 mg Injection, *n*-Heptane – IPA (84:16)



HPLC CONDITIONS

Column	: Alltech Econosil, 10 µm, 22 x 250 mm
Mobile Phase	: *n*-Heptane – Isopropyl Alcohol (84:16)
Flow Rate	: 10 mL/min
Run Time	: 65 min
Detection	: UV at 257 nm
Temperature	: Ambient
Injection Size	: ~50 mg
Dissolution	: 2 mL mobile phase plus ~ 0.75 mL ethyl alcohol
Retention Times	: **14** ~ 41 min
	: **14** ~ 54 min
	: Less Polar Impurity ~ Not resolved

Example Section F

Example F1

Phosphonic acid 2: To a solution of compound 1 (A. Flohr *et al.*, J. Med. Chem., 42, 12, 1999; 2633-2640) (4.45 g, 17 mmol) in CH_2Cl_2 (50 mL) at room temperature was added bromotrimethylsilane (1.16 mL, 98.6 mmol). The solution was stirred for 19 h. The volatiles were evaporated under reduced pressure to give the oily phosphonic acid 2 (3.44 g, 100%). ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5H), 4.61 (s, 2 H), 3.69 (d, 2H).

Example F2

Compound 3: To a solution of phosphonic acid 2 (0.67 g, 3.3 mmol) in CH_3CN (5 mL) was added thionyl chloride (1 mL, 13.7 mmol) and the solution was heated at 70°C for 2.5 h. The volatiles were evaporated under reduced pressure and dried in vacuo to afford an oily phophonyl dichloride. The crude chloride intermediate was dissolved in CH_2Cl_2 (20 mL) and cooled in an ice/water bath. Ethyl lactate (1.5 mL, 13.2 mmol) and triethyl amine (1.8 mL, 13.2 mmol) were added dropwise. The mixture was stirred for 4 h at room temperature and dilluted with more CH_2Cl_2 (100 mL). The organic solution was washed with 0.1N HCl, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$) filtered and evaporated under reduced pressure. The crude product was chromatographed on silica gel to afford oily compound 3 (0.548 g, 41%). ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5H), 5.00-5.20 (m, 2H), 4.65 (m, 2H), 4.20 (m, 4H), 3.90 (d, 2H), 1.52 (t, 6H), 1.20 (t, 6H).

Example F3

Alcohol 4: A solution of compound 3 (0.54 g, 1.34 mmol) in EtOH (15 mL) was treated with 10% Pd/C (0.1 g) under H_2 (100 psi) for 4 h. The mixture was filtered and the filtrate was treated with fresh 10% PD/C (0.1 g) under H_2 (1 atmosphere) for 18 h. The mixture was filtered and the filtrate was evaporated to afford alcohol 4 (0.395 g, 94%) as an oil. ^{1}H NMR ($CDCl_3$) δ 4.90-5.17 (m, 2H), 4.65 (q, 2H), 4.22 (m, 4H), 4.01 (m, 2H), 1.55 (t, 6H), 1.21 (t, 6H); ^{31}P NMR ($CDCl_3$) δ 22.8.

Example F4

Triflate 5: To a solution of alcohol 4 (122.8 mg, 0.393 mmol) in CH_2Cl_2 (5 mL) at -40°C were added 2,6-lutidine (0.069 mL, 0.59 mmol) and trifluoromethansulfonic anhydride (0.086 mL, 0.51 mmol). Stirring was continued at 0°C for 2 h. and the mixture partitioned in CH_2Cl_2 and saturated $NaHCO_3$. The organic layer was washed with 0.1N HCl, saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product 5 (150 mg, 87%) was used for the next step without further purification. ^1H NMR ($CDCl_3$) δ 5.0-5.20 (m, 2H), 4.93 (d, 2H), 4.22 (m, 4H), 1.59 (m, 6H), 1.29 (t, 6H).

Example F5

Phosphonate 6: A solution of phenol 8 (see Scheme Section A, Scheme A1 and A2) (32 mg, 0.055 mmol) and triflate 5 (50 mg, 0.11 mmol) in THF (1.5 mL) at room temperature was treated with Cs_2CO_3 (45.6 mg, 0.14 mmol). The mixture was stirred for 2.5 h and partitioned in EtOAc and saturated $NaHCO_3$. The organic layer was washed with 0.1N HCl, saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (30-70% EtOAc/hexane) affording the phosphonate 6 (41 mg, 84%) as a solid. ^1H NMR ($CDCl_3$) δ 7.71 (d, 2H), 7.13 (d, 2H), 7.00 (d, 2H), 6.90 (d, 2H), 5.65 (d, 1H), 4.90-5.22 (m, 3H), 4.40 (m, 2H), 4.20 (m, 4H), 3.90 (s, 3H), 3.65-4.00 (m, 5H), 2.70-3.20 (m, 6H), 1.52-1.87 (m, 12H), 1.25 (m, 6H), 0.85-0.90 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 20.0.

Example F6

Compound 7: To a solution of phosphonic acid 2 (0.48 g, 2.37 mmol) in CH_3CN (4 mL) was added thionyl chloride (0.65 mL, 9.48 mmol) and the solution was heated at 70°C for 2.5 h. The volatiles were evaporated under reduced pressure and dried in vacuo to afford an oily phophonyl dichloride. The crude chloride intermediate was dissolved in CH_2Cl_2 (5 mL) and cooled in an ice/water bath. Ethyl glycolate (0.9 mL, 9.5 mmol) and triethyl amine (1.3 mL, 9.5 mmol) were added dropwise. The mixture was stirred for 2 h at room temperature and dilluted with more CH_2Cl_2 (100 mL). The organic solution was washed with 0.1N HCl, saturated aqueous $NaHCO_3$, and saturated NaCl, dried ($MgSO_4$) filtered and concentrated under reduced pressure. The crude product was chromatographed on silica gel to afford oily compound 7 (0.223 g, 27%). ^1H NMR ($CDCl_3$) δ 7.30 (m, 5H), 4.65 (m, 6H), 4.25 (q, 4H), 3.96 (d, 2H), 1.27 (t, 6H); ^{31}P NMR ($CDCl_3$) δ 24.0.

Example F7

Alcohol 8: A solution of compound 7 (0.22 g, 0.65 mmol) in EtOH (8 mL) was treated with 10% Pd/C (0.04 g) under H_2 (1 atmosphere) for 4 h. The mixture was filtered and the filtrate was evaporated to afford alcohol 8 (0.156 g, 96%) as an oil. ^1H NMR ($CDCl_3$) δ 4.66 (m, 4H), 4.23 (q, 4H), 4.06 (d, 2H), 1.55 (t, 6H), 1.26 (t, 6H); ^{31}P NMR ($CDCl_3$) δ 26.8.

Example F8

Triflate 9: To a solution of alcohol 8 (156 mg, 0.62 mmol) in CH_2Cl_2 (5 mL) at -40°C were added 2,6-lutidine (0.11 mL, 0.93 mmol) and trifluoromethansulfonic anhydride (0.136 mL, 0.8 mmol). Stirring was continued at 0°C for 2 h. and the mixture partitioned in CH_2Cl_2 and saturated $NaHCO_3$. The organic layer was washed with 0.1N HCl, saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product 9 (210 mg, 88%) was used for the next step without further purification. ^1H NMR ($CDCl_3$) δ 4.90 (d, 2H), 4.76 (d, 4H), 4.27 (q, 4H), 1.30 (t, 6H).

Example F9

Phosphonate 10: A solution of phenol 8 (30 mg, 0.052 mmol) and triflate 9 (30 mg, 0.078 mmol) in THF (1.5 mL) at room temperature was treated with Cs_2CO_3 (34 mg, 0.1 mmol). The mixture was stirred for 2.5 h and partitioned in EtOAc and saturated $NaHCO_3$. The organic layer was washed with 0.1N HCl, saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (30-70% EtOAc/hexane) affording the unreacted phenol (xx) (12 mg, 40%) and the phosphonate 10 (16.6 mg, 38%) as a solid. ^1H NMR ($CDCl_3$) δ 7.71 (d, 2H), 7.13 (d, 2H), 7.00 (d, 2H), 6.90 (d, 2H), 5.65 (d, 1H), 5.00 (m, 2H), 4.75 (m, 4H), 4.48 (d, 2H), 4.23 (q, 4H), 3.90 (s, 3H), 3.65-4.00 (m, 5H), 2.70-3.20 (m, 6H), 2.23 (b.s., 2H), 1.52-1.87 (m, 4H), 1.25 (t, 6H), 0.85-0.90 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 22.0.

Example F10

Compound 11: To a solution of phosphonic acid 2 (0.512 g, 2.533 mmol) in CH_3CN (5 mL) was added thionyl chloride (0.74 mL, 10 mmol) and the solution was heated at 70°C for 2.5 h. The volatiles were evaporated under reduced pressure and dried in vacuo to afford an oily phophonyl dichloride. The crude chloride intermediate was dissolved in toluene (8 mL) and

cooled in an ice/water bath. A catalytic amount of tetrazol (16 mg, 0.21 mmol) was added followed by the addition of a solution of triethylamine (0.35 mL, 2.53 mmol) and phenol (238 mg, 2.53 mmol) in toluene (5 mL). The mixture was stirred at room temperature for 3 h. A solution of ethyl glycolate (0.36 mL, 3.8 mmol) and triethyl amine (0.53 mL, 3.8 mmol) in toluent (3 mL) was added dropwise. The mixture was stirred for 18 h at room temperature and partitioned in EtOAc and 0.1N HCl. The organic solution was washed with saturated aqueous $NaHCO_3$, and saturated NaCl, dried ($MgSO_4$) filtered and concentrated under reduced pressure. The crude product was chromatographed on silica gel to afford diphenyl phophonate as a byproduct (130 mg) and compound 11 (0.16 g, 18%). ^{1}H NMR ($CDCl_3$) δ 7.15-7.40 (m, 10H), 4.58-4.83 (m, 4H), 4.22 (q, 2H), 4.04 (dd, 2H), 1.24 (t, 3H).

Example F11

Alcohol 12: A solution of compound 11 (0.16 g, 0.44 mmol) in EtOH (5 mL) was treated with 10% Pd/C (0.036 g) under H_2 (1 atmosphere) for 22 h. The mixture was filtered and the filtrate was evaporated to afford alcohol 12 (0.112 g, 93%) as an oil. ^{1}H NMR ($CDCl_3$) δ 7.15-7.36 (m, 5H), 4.81 (dd, 1H), 4.55 (dd, 1H), 4.22 (q, 2H), 4.12 (m, 2H), 3.78 (b.s., 1H), 1.26 (t, 6H); ^{31}P NMR ($CDCl_3$) δ 22.9.

Example F12

Triflate 13: To a solution of alcohol 12 (112 mg, 0.41 mmol) in CH_2Cl_2 (5 mL) at -40°C were added 2,6-lutidine (0.072 mL, 0.62 mmol) and trifluoromethansulfonic anhydride (0.09 mL, 0.53 mmol). Stirring was continued at 0°C for 3 h. and the mixture partitioned in CH_2Cl_2 and saturated $NaHCO_3$. The organic layer was washed with 0.1N HCl, saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (30% EtOAc/hexane) affording triflate 13 (106 mg, 64%). ^{1}H NMR ($CDCl_3$) δ 7.36 (m, 2H), 7.25 (m, 3H), 4.80-5.10 (m, 3H), 4.60 (dd, 1H), 4.27 (q, 2H), 1.28 (t, 3H); ^{31}P NMR ($CDCl_3$) δ 11.1.

Example F13

Phosphonate 14: A solution of phenol 8 (32 mg, 0.052 mmol) and triflate 13 (32 mg, 0.079 mmol) in CH_3CN (1.5 mL) at room temperature was treated with Cs_2CO_3 (34 mg, 0.1 mmol). The mixture was stirred for 1 h and partitioned in EtOAc and saturated $NaHCO_3$. The

organic layer was washed with saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (70% EtOAc/hexane) affording phosphonate 14 (18 mg, 40%). ^1H NMR ($CDCl_3$) δ 7.71 (d, 2H), 6.75-7.35 (m, 11H, 5.65 (d, 1H), 5.00 (m, 2H), 4.50-4.88 (m, 3H), 4.20 (q, 2H), 3.84 (s, 3H), 3.65-4.00 (m, 5H), 2.70-3.20 (m, 6H), 1.52-1.87 (m, 6H), 1.25 (t, 3H), 0.85-0.90 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 17.9, 17.7.

Example F14

Piperidine 16: A solution of compound 15 (3.1 g, 3.673 mmol) in MeOH (100 mL) was treated with 10% Pd/C (0.35 g) under H_2 (1 atmosphere) for 18 h. The mixture was filtered and the filtrate was evaporated to afford phenol 16 (2 g, 88%). ^1H NMR (CD_3OD) δ 7.76 (d, 2H), 7.08 (d, 2H), 7.04 (d, 2H), 6.65 (d, 2H), 5.59 (d, 1H), 4.95 (m, 1H), 3.98 (s, 3H), 3.65-4.00 (m, 5H), 3.30-3.50 (m, 3H), 2.80-3.26 (m, 5H), 2.40-2.70 (m, 3H), 1.35-2.00 (m, 7H), 1.16 (m, 2H); MS (ESI) 620 (M+H).

Example F15

Formamide 17: Piperidine 16 obtained above (193 mg, 0.3118 mmol) in DMF (4 mL) was treated with formic acid (0.035 mL, 0.936 mmol), triethylamine (0.173 mL, 1.25 mmol) and EDCI (179 mg, 0.936 mmol) at room temperature. The mixture was stirred for 18 h and partitioned in EtOAc and saturated $NaHCO_3$. The organic layer was washed with saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (EtOAC/hexane) affording formamide 17 (162 mg, 80%). ^1H NMR ($CDCl_3$) δ 7.96 (s, 1H), 7.68 (d, 2H), 7.04 (d, 2H), 6.97 (d, 2H), 6.76 (d, 2H), 5.63 (d, 1H), 5.37 (bs, 1H), 5.04 (m, 1H), 4.36 (m, 1H), 3.93 (s, 3H), 3.52-3.95 (m, 7H), 2.70-3.20 (m, 8H), 1.48-2.00 (m, 7H), 1.02 (m, 2H).

Example F16

Dibenzyl phosphonate 18: A solution of phenol 17 (123 mg, 0.19 mmol) and dibenzyl trifluoromethansulfonyloxymethanphosphonate YY (120 mg, 0.28 mmol) in CH_3CN (1.5 mL) at room temperature was treated Cs_2CO_3 (124 mg, 0.38 mmol). The mixture was stirred for 3 h and partitioned in CH_2Cl_2 and saturated $NaHCO_3$. The organic layer was washed with 0.1N HCl, saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude

product was purified by chromatography on silica gel (10% $MeOH/CH_2Cl_2$) affording phosphonate 18 (154 mg, 88%). ^1H NMR ($CDCl_3$) δ 7.96 (s, 1H), 7.68 (d, 2H), 7.35 (m, 10H), 7.10 (d, 2H), 6.97 (d, 2H), 6.80 (d, 2H), 5.63 (d, 1H), 4.96-5.24 (m, 6H), 4.37 (m, 1H), 4.20 (d, 2H), 3.84 (s, 3H), 3.52-3.95 (m, 7H), 2.55-3.20 (m, 8H), 1.48-2.00 (m, 7H), 1.02 (m, 2H). ^{31}P NMR ($CDCl_3$) δ 20.3.

Example F17

Phosphonic acid 19: A solution of phosphonate 18 (24 mg, 0.026 mmol) in MeOH (3 mL) was treated with 10% Pd/C (5 mg) under H_2 (1 atmosphere) for 4 h. The mixture was filtered and the filtrate was evaporated to afford phosphonic acid 19 as a solid (18 mg, 93%). ^1H NMR (CD_3OD) δ 8.00 (s, 1H), 7.67 (d, 2H), 7.18 (d, 2H), 7.09 (d, 2H), 6.90 (d, 2H), 5.60 (d, 1H), 4.30 (m, 1H), 4.16 (d, 2H), 3.88 (s, 3H), 3.60-4.00 (m, 7H), 3.04-3.58 (m, 5H), 2.44-2.92 (m, 5H), 1.28-2.15 (m, 5H), 1.08 (m, 2H). ^{31}P NMR ($CDCl_3$) δ 16.3.

Example F18

Diethyl phosphonate 20: A solution of phenol 17 (66 mg, 0.1 mmol) and diethyl trifluoromethansulfonyloxymethanphosphonate XY (46 mg, 0.15mmol) in CH_3CN (1.5 mL) at room temperature was treated Cs_2CO_3 (66 mg, 0.2 mmol). The mixture was stirred for 3 h and partitioned in CH_2Cl_2 and saturated $NaHCO_3$. The organic layer was washed with 0.1N HCl, saturated NaCl, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (10% $MeOH/CH_2Cl_2$) affording the unreacted 17 (17 mg, 26%) and diethyl phosphonate 20 (24.5 mg, 41%). ^1H NMR ($CDCl_3$) δ 8.00 (s, 1H), 7.70 (d, 2H), 7.16 (d, 2H), 7.00(d, 2H), 6.88 (d, 2H), 5.66 (d, 1H), 4.98-5.10 (m, 2H), 4.39 (m, 1H), 4.24 (m, 5H), 3.89 (s, 3H), 3.602-3.98 (m, 7H), 2.55-3.16 (m, 8H), 1.50-2.00 (m, 7H), 1.36 (t, 6H), 1.08 (m, 2H). ^{31}P NMR ($CDCl_3$) δ 19.2.

Example F19

N-methyl pepiridine diethyl phosphonate 21: A solution of compound 20 (22.2 mg, 0.0278 mmol) in THF (1.5 mL) at 0°C was treated with a solution of borane in THF (1M, 0.083 mL). The mixture was stirred for 2 h at room temperature and the starting material was consumed completely as monitored by TLC. The reaction mixture was cooled in an ice/water bath and excess methanol (1 mL) was added to quench the reaction. The solution was

concentrated in vacuo and the crude product was chromatographed on silica gel with MeOH/EtOAc to afford compound 21 (7 mg, 32%). ^{1}H NMR ($CDCl_3$) δ 7.70 (d, 2H), 7.16 (d, 2H), 7.00(d, 2H), 6.88 (d, 2H), 5.66 (d, 1H), 4.98-5.10 (m, 2H), 4.24 (m, 4H), 3.89 (s, 3H), 3.602-3.98 (m, 7H), 2.62-3.15 (m, 9H), 2.26 (s, 3H), 1.52-2.15 (m, 10H), 1.36 (t, 6H). ^{31}P NMR ($CDCl_3$) δ 19.3.

Example Section G

Example G1

Compound 1: To a solution of 4-nitrobenzyl bromide (21.6 g, 100 mmol) in toluene (100 mL) was added triethyl phosphite (17.15 mL, 100 mL). The mixture was heated at 120°C for 14 hrs. The evaporation under reduced pressure gave a brown oil, which was purified by flash column chromatography (hexane/EtOAc= 2/1 to 100 % EtOAc) to afford compound 1.

Example G2

Compound 2: To a solution of compound 1 (1.0 g) in ethanol (60 mL) was added 10% Pd-C (300 mg). The mixture was hydrogenated for 14 hrs. Celite was added and the mixture was stirred for 5 mins. The mixture was filtered through a pad of celite, and washed with ethanol. Concentration gave compound 2.

Example G3

Compound 3: To a solution of compound 3 (292 mg, 1.2 mmol) and aldehyde (111 mg, 0.2 mmol) in methanol (3 mL) was added acetic acid (48 μL, 0.8 mmol). The mixture was stirred for 5 mins, and sodium cyanoborohydride (25 mg, 0.4 mmol) was added. The mixture was stirred for 14 hrs, and methanol was removed under reduced pressure. Water was added, and was extracted with EtOAc. The organic phase was washed 0.5 N NaOH solution (1x), water (2x), and brine (1x), and was dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/MeOH = 100/3) gave compound 3.

Example G4

Compound 4: To a solution of compound 3 (79 mg , 0.1 mmol) in CH_2Cl_2 (5 mL) was added trifluoroacetic acid (1 mL). The mixture was stirred for 2 hrs, and solvents were evaporated under reduced pressure. Coevaporation with EtOAc and CH_2Cl_2 gave an oil. The oil was dissolved in THF (1mL) and tetrabutylamonium fluoride (0.9 mL, 0.9 mmol) was added. The mixture was stirred for 1 hr, and solvent was removed. Purification by flash column chromotogaphy (CH_2Cl_2/MeOH = 100/7) gave compound 4.

Example G5

Compound 5: To a solution of compound 4 (0.1 mmol) in acetonitrile (1 mL) at 0°C was added DMAP (22 mg, 0.18 mmol), followed by bisfurancarbonate (27 mg, 0.09 mmol). The mixture was stirred for 3 hrs at 0°C, and diluted with EtOAc. The organic phase was washed with 0.5 N NaOH solution (2x), water (2x), and brine (1x), and dried over $MgSO_4$. Purification by flash column chromotography (CH_2Cl_2/MeOH = 100/3 to 100/5) afford compound 5 (50 mg): ^1H NMR ($CDCl_3$) δ 7.70 (2 H, d, J = 8.9 Hz), 7.11 (2 H, d, J = 8.5 Hz), 6.98 (2 H, d, J = 8.9 Hz), 6.61 (2 H, d, J = 8.5 Hz), 5.71 (1 H, d, J = 5.2 Hz), 5.45 (1 H, m), 5.13 (1 H, m), 4.0 (6 H, m), 3.98-3.70 (4 H, m), 3.86 (3 H, s), 3.38 (2 H, m), 3.22 (1 H, m), 3.02 (5 H, m), 2.8 (1 H, m), 2.0-1.8 (3 H, m), 1.26 (6 H, t, J = 7.0 Hz), 0.95 (3 H, d, J = 6.7 Hz), 0.89 (3 H, d, J = 6.7 Hz).

Example G6

Compound 6: To a solution of compound 5 (30 mg, 0.04 mmol) in MeOH (0.8 mL) was added 37% fomaldehyde (30 μL, 0.4 mmol), followed by acetic acid (23 μL, 0.4 mmol). The mixture was stirred for 5 mins, and sodium cyanoborohydride (25 mg, 0.4 mmol) was added. The reaction mixture was stirred for 14 hrs, and diluted with EtOAc. The organic phase was washed 0.5 N NaOH solution (2x), water (2x), and brine, and dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/MeOH = 100/3) gave compound 6 (11 mg): ^1H NMR ($CDCl_3$) δ 7.60 (2 H, d, J = 8.9 Hz), 7.17 (2 H, m), 6.95 (2 H, d, J = 8.9 Hz), 6.77 (2 H, d, J = 8.5 Hz), 5.68 (1 H, d, J = 5.2 Hz), 5.21 (1 H, m), 5.09 (1 H, m), 4.01 (6 H, m), 3.87 (3 H, s), 3.8-3.3 (4 H, m), 3.1-2.6 (7 H, m), 2.90 (3 H, s), 1.8 (3 H, m), 1.25 (6 H, m), 0.91 (6 H, m).

Example G7

Compound 7: To a solution of compound 1 (24.6 g, 89.8 mmol) in acetonitrile (500 mL) was added TMSBr (36 mL, 269 mmol). The reaction mixture was stirred for 14 hrs, and evaporated under reduced pressure. The mixture was coevaporated with MeOH (2x), toluene (2x), EtOAc (2x), and CH_2Cl_2 to give a yellow solid (20 g). To the suspension of above yellow solid (15.8 g, 72.5 mmol) in toluene (140 mL) was added DMF (1.9 mL), followed by thionyl chloride (53 mL, 725 mmol). The reaction mixture was heated at 60°C for 5 hrs, and evaporated under reduced pressure. The mixture was coevaporated with toluene (2x), EtOAc, and CH_2Cl_2 (2x) to afford a brown solid. To the solution of the brown solid in CH_2Cl_2 at 0°C was added benzyl alcohol (29 mL, 290 mmol), followed by slow addition of pyridine (35 mL, 435 mmol).

The reaction mixture was allowed to warm to 25°C and stirred for 14 hrs. Solvents were removed under reduced pressure. The mixture was diluted with EtOAc, and washed with water (3x) and brine (1x), and dried over $MgSO_4$. Concentration gave a dark oil, which was purified by flash column chromatography (hexanes/EtOAc = 2/1 to 1/1) to afford compound 7.

Example G8

Compound 8: To a solution of compound 7 (15.3 g) in acetic acid (190 mL) was added Zinc dust (20 g). The mixture was stirred for 14 hrs, and celite was added. The suspension was filtered through a pad of celite, and washed with EtOAc. The solution was concentrated under reduced pressure to dryness. The mixture was diluted with EtOAc, and was washed with 2N NaOH (2x), water (2x), and brine (1x), and dried over $MgSO_4$. Concentration under reduced pressure gave compound 8 as an oil (15 g).

Example G9

Compound 9: To a solution of compound 8 (13.5 g, 36.8 mmol) and aldehyde (3.9 g, 7.0 mmol) in methanol (105 mL) was added acetic acid (1.68 mL, 28 mmol). The mixture was stirred for 5 mins, and sodium cyanoborohydride (882 mg, 14 mmol) was added. The mixture was stirred for 14 hrs, and methanol was removed under reduced pressure. Water was added, and was extracted with EtOAc. The organic phase was washed 0.5 N NaOH solution (1x), water (2x), and brine (1x), and was dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/MeOH = 100/3) gave compound 9 (6.0 g).

Example G10

Compound 10: To a solution of compound 9 (6.2 g , 6.8 mmol) in CH_2Cl_2 (100 mL) was added trifluoroacetic acid (20 mL). The mixture was stirred for 2 hrs, and solvents were evaporated under reduced pressure. Coevaporation with EtOAc and CH_2Cl_2 gave an oil. The oil was dissolved in THF (1mL) and tetrabutylamonium fluoride (0.9 mL, 0.9 mmol) was added. The mixture was stirred for 1 hr, and solvent was removed. Purification by flash column chromotogaphy (CH_2Cl_2/MeOH = 100/7) gave compound 10.

Example G11

Compound 11: To a solution of compound 10 (5.6 mmol) in acetonitrile (60 mL) at 0°C was added DMAP (1.36g, 11.1 mmol), followed by bisfurancarbonate (1.65 g, 5.6 mmol). The

mixture was stirred for 3 hrs at 0°C, and diluted with EtOAc. The organic phase was washed with 0.5 N NaOH solution (2x), water (2x), and brine (1x), and dried over $MgSO_4$. Purification by flash column chromotography (CH_2Cl_2/MeOH = 100/3 to 100/5) afford compound 11 (3.6 g): ^{1}H NMR ($CDCl_3$) δ 7.70 (2 H, d, J = 8.9 Hz), 7.30 (10 H, m), 7.07 (2 H, m), 6.97 (2 H, d, J = 8.9 Hz), 6.58 (2 H, d, J = 8.2 Hz), 5.70 (1 H, d, J = 5.2 Hz), 5.42 (1 H, m), 5.12 (1 H, m), 4.91 (4 H, m), 4.0-3.7 (6 H, m), 3.85 (3 H, s), 3.4 (2 H, m), 3.25 (1 H, m), 3.06 (2 H, d, J = 21 Hz), 3.0 (3 H, m), 2.8 (1 H, m), 1.95 (1 H, m), 1.82 (2 H, m), 0.91 (6 H, m).

Example G12

Compound 12: To a solution of compound 11 (3.6 g) in ethanol (175 mL) was added 10% Pd-C (1.5 g). The reaction mixture was hydrogenated for 14 hrs. The mixture was stirred with celite for 5 mins, and filtered through a pad of celite. Concentration under reduced pressure gave compound 12 as a white solid (2.8 g): ^{1}H NMR (DMSO-d_6) δ 7.68 (2 H, m), 7.08 (2 H, m), 6.93 (2 H, m), 6.48 (2 H, m), 5.95 (1 H, m), 5.0 (2 H, m), 3.9-3.6 (6 H, m), 3.82 (3 H, s), 3.25 (3 H, m), 3.05 (4 H, m), 2.72 (2 H, d, J = 20.1 Hz), 2.0-1.6 (3 H, m), 0.81 (6 H, m).

Example G13

Compound 13: Compound 12 (2.6 g, 3.9 mmol) and L-alanine ethyl ester hydrochloride (3.575 g, 23 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in pyridine (20 mL) and diisopropylethylamine (4.1 mL, 23 mmol) was added. To above mixture was added a solution of Aldrithiol (3.46 g, 15.6 mmol) and triphenylphosphine (4.08 g, 15.6 g) in pyridine (20 mL). The reaction mixture was stirred for 20 hrs, and solvents were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with 0.5 N NaOH solution (2x), water (2x), and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave a yellow oil, which was purified by flash column chromatography (CH_2Cl_2/MeOH = 100/5 to100/10) to afford compound 13 (750 mg): ^{1}H NMR ($CDCl_3$) δ 7.71 (2 H, d, J = 8.8 Hz), 7.13 (2 H, m), 6.98 (2 H, d, J = 8.8 Hz), 6.61 (2 H, d, J = 8.0 Hz), 5.71 (1 H, d, J = 5.2 Hz), 5.54 (1 H, m), 5.16 (1 H, m), 4.15 (6 H, m), 4.1-3.6 (6 H, m), 3.86 (3 H, s), 3.4-3.2 (3 H, m), 3.1-2.8 (8 H, m), 2.0 (1 H, m), 1.82 (2 H, m), 1.3 (12 H, m), 0.92 (6 H, m).

Example G14

Compound 14: To a solution of 4-hydroxypiperidine (19.5 g, 193 mmol) in THF at 0°C was added sodium hydroxide solution (160 mL, 8.10 g, 203 mmol), followed by di-tert-butyl dicarbonate (42.1 g, 193 mmol). The mixture was warmed to 25°C, and stirred for 12 hours. THF was removed under reduced pressure, and the aqueous phase was extracted with EtOAc (2x). The combined organic layer was washed with water (2x) and brine, and dried over MgSO4. Concentration gave a compound 14 as a white solid (35 g).

Example G15

Compound 15: To a solution of alcohol 14 (5.25 g, 25 mmol) in THF (100 mL) was added sodium hydride (1.2 g, 30 mmol, 60%). The suspension was stirred for 30 mins, and chloromethyl methyl sulfide (2.3 mL, 27.5 mmol) was added. Starting material alcohol 14 still existed after 12 hrs. Dimethy sulfoxide (50 mL) and additional chloromethyl methyl sulfide (2.3 mL, 27.5 mmol) were added. The mixture was stirred for additional 3 hrs, and THF was removed under reduced pressure. The reaction was quenched with water, and extracted with ethyl acetate. The organic phase was washed with water and brine, and was dried over $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 8/1) gave compound 15 (1.24 g).

Example G16

Compound 16: To a solution of compound 15 (693 mg, 2.7 mmol) in CH_2Cl_2 (50 mL) at –78°C was added a solution of sulfuryl chloride (214 μL, 2.7 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was kept at –78°C for 3 hrs, and solvents were removed to give a white solid. The white solid was dissolved in toluene (7 mL), and triethyl phosphite (4.5 mL, 26.6 mmol) was added. The reaction mixture was heated at 120°C for 12 hrs. Solvent and excess reagent was removed under reduced pressure to give compound 16.

Example G17

Compound 17: To a solution of compound 17 (600 mg) in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred for 2 hrs, and was concentrated under reduced pressure to give an oil. The oil was diluted with methylene chloride and base resin was

added. The suspension was filtered and the organic phase was concentrated to give compound 17.

Example G18

Compound 18: To a solution of compound 17 (350 mg, 1.4 mmol) and aldehyde (100 mg, 0.2 mmol) in methanol (4 mL) was added acetic acid (156 μL, 2.6 mmol). The mixture was stirred for 5 mins, and sodium cyanoborohydride (164 mg, 2.6 mmol) was added. The mixture was stirred for 14 hrs, and methanol was removed under reduced pressure. Water was added, and was extracted with EtOAc. The organic phase was washed 0.5 N NaOH solution (1x), water (2x), and brine (1x), and was dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/MeOH = 100/3) gave compound 18 (62 mg).

Example G19

Compound 19: To a solution of compound 18 (62 mg, 0.08 mmol) in THF (3 mL) were added acetic acid (9 μL, 0.15 mmol) and tetrabutylamonium fluoride (0.45 mL, 1.0 N, 0.45mmol). The mixture was stirred for 3 hr, and solvent was removed. Purification by flash column chromotogaphy (CH_2Cl_2/MeOH = 100/5) gave an oil. To a solution of above oil in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred for 1 hrs, and was concentrated under reduced pressure. Coevaporation with EtOAc and CH_2Cl_2 gave compound 19.

Example G20

Compound 20: To a solution of compound 19 (55 mg 0.08 mmol) in acetonitrile (1 mL) at 0°C was added DMAP (20 mg, 0.16 mmol), followed by bisfurancarbonate (24 mg, 0.08 mmol). The mixture was stirred for 3 hrs at 0°C, and diluted with EtOAc. The organic phase was washed with 0.5 N NaOH solution (2x), water (2x), and brine (1x), and dried over $MgSO_4$. Purification by flash column chromotography (CH_2Cl_2/MeOH = 100/3 to 100/5) afford compound 20 (46 mg): ^{1}H NMR ($CDCl_3$) δ 7.70 (2 H, d, J = 8.9 Hz), 7.01 (2 H, d, J = 8.9 Hz), 5.73 (1 H, d, J = 5.1 Hz), 5.51 (1 H, m), 5.14 (1 H, m), 4.16 (1 H, m), 4.06 (1 H, m), 3.94 (3 H, m), 3.86 (3 H, s), 3.80 (1 H, m), 3.75 (2 H, d, J = 9.1 Hz), 3.58 (1 H, m), 3.47 (1 H, m), 3.30 (1 H, m), 3.1-2.6 (8 H, m), 2.3 (2 H, m), 2.1-1.8 (5 H, m), 1.40 (2 H, m), 1.36 (6 H, t, J = 7.0 Hz), 0.93 (3 H, d, J = 6.7 Hz), 0.86 (3 h, d, J = 6.7 Hz).

Example G21

Compound 21: Compound 21 was made from Boc-4-Nitro-L-Phenylalanine (Fluka) following the procedure for Compound 2 in Scheme Section A, Scheme A1.

Example G22

Compound 22: To a solution of chloroketone 21 (2.76 g, 8 mmol) in THF (50 mL) and water (6 mL) at 0°C (internal temperature) was added solid $NaBH_4$ (766 mg, 20 mmol) in several portions over a period of 15 min while maintaining the internal temperature below 5°C. The mixture was stirred for 1.5 hrs at 0°C and solvent was removed under reduced pressure. The mixture was quenched with saturated $KHSO_3$ and extracted with EtOAc. The organic phase was washed with waster and brine, and dried over$MgSO_4$. Concentration gave a solid, which was recrystalized from EtOAc/hexane (1/1) to afford the chloroalcohol 22 (1.72 g).

Example G23

Compound 23: To a suspension of chloroalcohol 22 (1.8 g, 5.2 mmol) in EtOH (50 mL) was added a solution of KOH in ethanol (8.8 mL, 0.71 N, 6.2 mmol). The mixture was stirred for 2 h at room temperature and ethanol was removed under reduced pressure. The reaction mixture was diluted with EtOAc, and washed with water (2x), saturated NH_4Cl (2x), water, and brine, and dried over $MgSO_4$. Concentration under reduced pressure afforded epoxide 23 (1.57g) as a white crystalline solid.

Example G24

Compound 24: To a solution of epoxide 23 (20 g, 65 mmol) in 2-propanol (250 mL) was added isobutylamine (65 mL) and the solution was refluxed for 90 min. The reaction mixture was concentrated under reduced pressure and was coevaporated with MeOH, CH_3CN, and CH_2Cl_2 to give a white solid. To a solution of the white solid in CH_2Cl_2 (300 mL) at 0°C was added triethylamine (19 mL, 136 mmol), followed by the addition of 4-methoxybenzenesulfonyl chloride (14.1 g, 65 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was stirred at 0°C for 30 min, and warmed to room temperature and stirred for additional 2 hrs. The reaction solution was concentrated under reduced pressure and was diluted with EtOAc. The organic phase was washed with saturated $NaHCO_3$, water and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave compound 24 as a white solid (37.5 g).

Example G25

Compound 25: To a solution of compound 24 (37.5 g, 68 mmol) in CH_2Cl_2 (100 mL) at 0°C was added a solution of tribromoborane in CH_2Cl_2 (340 mL, 1.0 N, 340 mmol). The reaction mixture was kept at 0°C for 1 hr, and warmed to room temperature and stirred for additional 3 hrs. The mixture was cooled to 0°C, and methanol (200 mL) was added slowly. The mixture was stirred for 1 hr and solvents were removed under reduced pressure to give a brown oil. The brown oil was coevaporated with EtOAc and toluene to afford compound 25 as a brown solid, which was dried under vacuum for 48 hrs.

Example G26

Compound 26: To a solution of compound 25 in THF (80 mL) was added a saturated sodium bicarbonate solution (25 mL), followed by a solution of Boc2O (982 mg, 4.5 mmol) in THF (20 mL). The reaction mixture was stirred for 5 hrs. THF was removed under reduced pressure, and aqueous phase was extracted with EtOAc. The organic phase was washed with water (2x) and Brine (1x), and dried over $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 1/1) gave compound 26 (467 mg).

Example G27

Compound 27: To a solution of compound 26 (300 mg, 0.56 mmol) in THF (6 mL) was added Cs_2CO_3 (546 mg, 1.68 mmol), followed by a solution of triflate (420 mg, 1.39 mmol) in THF (2 mL). The reaction mixture was stirred for 1.5 hrs. The mixture was diluted with EtOAc, and washed with water (3x) and brine (1x), and dried over $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 1/1 to 1/3) gave compound 27 (300 mg).

Example G28

Compound 28: To a solution of compound 27 (300 mg, 0.38 mmol) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred for 2.5 hrs, and was concentrated under reduced pressure. The mixture was diluted with EtOAc and was washed with 0.5 N NaOH solution (3x), water (2x), and brine (1x), and dried over $MgSO_4$. Concentration gave a white solid. To the solution of above white solid in acetonitrile (3 mL) at 0°C was added DMAP (93 mg, 0.76 mmol), followed by bisfurancarbonate (112 mg, 0.38 mmol). The mixture was stirred for 3 hrs at 0°C, and diluted with EtOAc. The organic phase was washed with 0.5 N NaOH

solution (2x), water (2x), and brine (1x), and dried over $MgSO_4$. Purification by flash column chromotography (CH_2Cl_2/MeOH = 100/3 to 100/5) afford compound 28 (230 mg): ^1H NMR ($CDCl_3$) δ 8.16 (2 H, d, J = 8.5 Hz), 7.73 (2 H, d, J = 9.2 Hz), 7.42 (2 H, d, J = 8.5 Hz), 7.10 (2 H, d, J = 9.2 Hz), 5.65 (1 H,d, J = 4.8 Hz), 5.0 (2 H, m), 4.34 (2 H, d, J = 10 Hz), 4.25 (4 H, m), 4.0-3.6 (6 H, m), 3.2-2.8 (7 H, m), 1.82 (1 H, m), 1.6 (2 H, m), 1.39 (6 H, t, J = 7.0 Hz), 0.95 (6 H, m).

Example G29

Compound 29: To a solution of compound 28 (50 mg) in ethanol (5 mL) was added 10% Pd-C (20 mg). The mixture was hydrogenated for 5 hrs. Celite was added, and the mixture was stirred for 5 mins. The reaction mixture was filtered through a pad of celite. Concentration under reduced pressure gave compound 29 (50 mg): ^1H NMR ($CDCl_3$) δ 7.72 (2 H, d, J = 8.8 Hz), 7.07 (2 H, 2 H, d, J = 8.8 Hz), 7.00 (2 H, d, J = 8.5 Hz), 6.61 (2 H, d, J = 8.5 Hz), 5.67 (1 H, d, J = 5.2 Hz), 5.05 (1 H, m), 4.90 (1 H, m), 4.34 (2 H, d, J = 10.3 Hz), 4.26 (2 H, m), 4.0-3.7 (6 H, m), 3.17 (1 H, m), 2.95 (4 H, m), 2.75 (2 H, m), 1.82 (1 H, m), 1.65 (2 H, m), 1.39 (6 H, t, J = 7.0 Hz), 0.93 (3 h, d, J = 6.4 Hz), 0.87 (3 h, d, J = 6.4 Hz).

Example G30

Compound 30: To a solution of compound 29 (50 mg, 0.07 mmol) and formaldehyde (52 μL, 37%, 0.7 mmol) in methanol (1 mL) was added acetic acid (40 μL, 0.7 mmol). The mixture was stirred for 5 mins, and sodium cyanoborohydride (44 mg, 0.7 mmol) was added. The mixture was stirred for 14 hrs, and methanol was removed under reduced pressure. Water was added, and was extracted with EtOAc. The organic phase was washed 0.5 N NaOH solution (1x), water (2x), and brine (1x), and was dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/MeOH = 100/3) gave compound 30 (40 mg): ^1H NMR ($CDCl_3$) δ 7.73 (2 H, d, J = 8.9 Hz), 7.10 (4 H, m), 6.66 (2 H, d, J = 8.2 Hz), 5.66 (1 H, d, J = 5.2 Hz), 5.02 (1 H, m), 4.88 (1 H, m), 4.32 (2 H, d, J = 10.1 Hz), 4.26 (4 H, m), 3.98 (1 H, m), 3.85 (3 H, m), 3.75 (2 H, m), 3.19 (1 H, m), 2.98 (4 H, m), 2.93 (6 H, s), 2.80 (2 H, m), 1.82 (1 H, m), 1.62 (2 H, m), 1.39 (6 H, t, J = 7.0 Hz), 0.90 (6 H, m).

Example G31

Compound 31: To a suspension of compound 25 (2.55 g, 5 mmol) in CH_2Cl_2 (20 mL) at 0°C was added triehtylamine (2.8 mL, 20 mmol), followed by TMSCl (1.26 mL, 10 mmol). The mixture was stirred at 0°C for 30 mins, and warmed to 25°C and stirred for additional 1 hr. Concentration gave a yellow solid. The yellow solid was dissolved in acetonitrile (30 mL) and cooled to 0°C. To this solution was added DMAP (1.22 g, 10 mmol) and Bisfurancarbonate (1.48 g, 5 mmol). The reaction mixture was stirred at 0°C for 2 hrs and for additional 1 hr at 25°C. Acetonitrile was removed under reduced pressure. The mixture was diluted with EtOAc, and washed with 5% citric acid (2x), water (2x), and brine (1x), and dried over $MgSO_4$. Concentration gave a yellow solid. The yellow solid was dissolved in THF (40 mL), and acetic acid (1.3 mL, 20 mmol) and tetrabutylammonium fluoride (8mL, 1.0 N, 8mmol) were added. The mixture was stirred for 20 mins, and THF was removed under reduced pressure. Purification by flash column chromatography (hexenes/EtOAc = 1/1) gave compound 31 (1.5 g).

Example G32

Compound 32: To a solution of compound 31 (3.04 g, 5.1 mmol) in THF (75 mL) was added Cs_2CO_3 (3.31 g, 10.2 mmol), followed by a solution of triflate (3.24 g, 7.65 mmol) in THF (2 mL). The reaction mixture was stirred for 1.5 hrs, and THF was removed under reduced pressure. The mixture was diluted with EtOAc, and washed with water (3x) and brine (1x), and dried over $MgSO_4$. Purification by flash column chromatography (hexanes/EtOAc = 1/1 to 1/3) gave compound 32 (2.4 g): ^1H NMR ($CDCl_3$) δ 8.17 (2 H, d, J = 8.5 Hz), 7.70 (2 H, J = 9.2 Hz), 7.43 (2 H, d, J = 8.5 Hz), 7.37 (10 H, m), 6.99 (2 H, d, J =9.2 Hz), 5.66 (1 H, d, J = 5.2 Hz), 5.15 (4 H, m), 5.05 (2 H, m), 4.26 (2 H, d, J = 10.2 Hz), 3.9-3.8 (4 H, m), 3.75 (2 H, m), 3.2-2.8 (7 H, m), 1.82 (1 H, m), 1.62 (2 H, m), 0.92 (6 H, m).

Example G33

Compound 33: To a solution of compound 32 (45 mg) in acetic acid (3 mL) was added zinc (200 mg). The mixture was stirred for 5 hrs. Celite was added, and the mixture was filtered and washed with EtOAc. The solution was concentrated to dryness and diluted with EtOAc. The organic phase was washed with 0.5 N NaOH solution, water, and brine, and dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/isoproanol = 100/5) gave

compound 33 (25 mg): ^{1}H NMR ($CDCl_3$) δ 7.67 (2 H, d, J = 8.8 Hz), 7.36 (10 H, m), 6.98 (4 H, m), 6.60 (2 H, d, J = 8.0 Hz), 5.67 (1 H, d, J = 4.9 Hz), 5.12 (4 H, m), 5.05 (1 H, m), 4.90 (1 H, m), 4.24 (2 H, d, J = 10.4 Hz), 4.0-3.6 (6 H, m), 3.12 (1 H, m), 3.95 (4 H, m), 2.75 (2 H, m), 1.80 (1 H, m), 1.2 (2 H, m), 0.9 (6 H, m).

Example G34

Compound 34: To a solution of compound 32 (2.4 g) in ethanol (140 mL) was added 10% Pd-C (1.0 g). The mixture was hydrogenated for 14 hrs. Celite was added, and the mixture was stirred for 5 mins. The slurry was filtered through a pad of celite, and washed with pyridine. Concentration under reduced pressure gave compound 34: ^{1}H NMR (DMSO-d_6) δ 7.67 (2 H, d, J = 8.9 Hz), 7.14 (2 H, d, J = 8.9 Hz), 6.83 (2 H, d, J = 8.0 Hz), 6.41 (2 H, d, J = 8.0 Hz), 5.51 (1 H, d, J = 5.2 Hz), 5.0-4.8 (2 H, m), 4.15 (2 H, d, J = 10.0 Hz), 3.9-3.2 (8 H, m), 3.0 (2 H, m), 2.8 (4 H, m), 2.25 (1 H, m), 1.4 (2 H, m), 0.8 (6 H, m).

Example G35

Compound 35: Compound 34 (1.62 g, 2.47 mmol) and L-alanine butyl ester hydrochloride (2.69 g, 14.8 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in pyridine (12 mL) and diisopropylethylamine (2.6 mL, 14.8 mmol) was added. To above mixture was added a solution of Aldrithiol (3.29 g, 14.8 mmol) and triphenylphosphine (3.88 g, 14.8 g) in pyridine (12 mL). The reaction mixture was stirred for 20 hrs, and solvents were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with 0.5 N NaOH solution (2x), water (2x), and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave a yellow oil, which was purified by flash column chromatography (CH_2Cl_2/MeOH = 100/5 to100/15) to afford compound 35 (1.17 g): ^{1}H NMR ($CDCl_3$) δ 7.70 (2 H, d, J = 8.6 Hz), 7.05 (2 H, d, J =8.6 Hz), 6.99 (2 H, d, J = 8.0 Hz), 6.61 (2 H, d, J = 8.0 Hz), 5.67 (1 H, d, J = 5.2 Hz), 5.05 (1 H, m), 4.96 (1 H, m), 4.28 (2 H, m), 4.10 (6 H, m), 4.0-3.6 (6 H, m), 3.12 (2 H, m), 2.92 (3 H, m), 2.72 (2 H, m), 1.82 (1 H, m), 1.75-1.65 (2 H, m), 1.60 (4 H, m), 1.43 (6 H, m), 1.35 (4 H, m), 0.91 (12 H, m).

Example G36

Compound 37: Compound 36 (100 mg, 0.15 mmol) and L-alanine butyl ester hydrochloride (109 mg, 0.60 mmol) were coevaporated with pyridine (2x). The mixture was

dissolved in pyridine (1 mL) and diisopropylethylamine (105 μL, 0.6 mmol) was added. To above mixture was added a solution of Aldrithiol (100 mg, 0.45 mmol) and triphenylphosphine (118 mg, 0.45 mmol) in pyridine (1 mL). The reaction mixture was stirred for 20 hrs, and solvents were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with water (2x), and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave an oil, which was purified by flash column chromatography (CH_2Cl_2/MeOH = 100/5 to100/15) to afford compound 37 (21 mg): ^{1}H NMR ($CDCl_3$) δ 7.71 (2 H, d, J = 8.8 Hz), 7.15 (2 H, d, J = 8.2 Hz), 7.01 (2 H, d, J = 8.8 Hz), 6.87 (2 H, d, J = 8.2 Hz), 5.66 (1 H, d, J = 5.2 Hz), 5.03 (1 H, m), 4.95 (1 H, m),4.2-4.0 (8 H, m), 3.98 (1 H, m), 3.89 (3 H, s), 3.88-3.65 (5 H, m), 3.15 (1 H, m), 2.98 (4 H, m), 2.82 (2 H, m), 1.83 (1 H, m), 1.63 (4 H, m), 1.42 (6 H, m), 1.35 (4 H, m), 0.95 (12 H, m).

Example G37

Compound 38: Compound 36 (100 mg, 0.15 mmol) and L-leucine ethyl ester hydrochloride (117 mg, 0.60 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in pyridine (1 mL) and diisopropylethylamine (105 μL, 0.6 mmol) was added. To above mixture was added a solution of Aldrithiol (100 mg, 0.45 mmol) and triphenylphosphine (118 mg, 0.45 mmol) in pyridine (1 mL). The reaction mixture was stirred for 20 hrs, and solvents were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with water (2x), and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave an oil, which was purified by flash column chromatography (CH_2Cl_2/MeOH = 100/5 to100/15) to afford compound 38 (12 mg): ^{1}H NMR ($CDCl_3$) δ 7.72 (2 H, d, J = 8.5 Hz), 7.14 (2 H, d, J = 8.0 Hz), 7.00 (2 H, d, J = 8.5 Hz), 6.86 (2 H, d, J = 8.0 Hz), 5.66 (1 H, d, J = 5.2 Hz), 5.05 (1 H, m), 4.95 (1 H, m), 4.2-4.0 (8 H, m), 4.0-3.68 (6 H, m), 3.88 (3 H, s), 3.2-2.9 (5 H, m), 2.80 (2 H, m), 1.80 (1 H, m), 1.65 (4 H, m), 1.65-1.50 (4 H, m), 1.24 (6 H, m), 0.94 (18 H, m).

Example G38

Compound 39: Compound 36 (100 mg, 0.15 mmol) and L-leucine butyl ester hydrochloride (117 mg, 0.60 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in pyridine (1 mL) and diisopropylethylamine (105 μL, 0.6 mmol) was added. To above mixture was added a solution of Aldrithiol (100 mg, 0.45 mmol) and triphenylphosphine

(118 mg, 0.45 mmol) in pyridine (1 mL). The reaction mixture was stirred for 20 hrs, and solvents were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with water (2x), and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave an oil, which was purified by flash column chromatography (CH_2Cl_2/MeOH = 100/5 to100/15) to afford compound 39 (32 mg): ^1H NMR ($CDCl_3$) δ 7.72 (2 H, d, J = 8.8 Hz), 7.15 (2 H, d, J = 8.0 Hz), 7.0 (2 H, d, J = 8.8 Hz), 6.89 (2 H, d, J = 8.0 Hz), 5.66 (1 H, d, J = 4.3 Hz), 5.07 (1 H, m), 4.94 (1 H, m), 4.2-4.0 (8 H, m), 3.89 (3 H, s), 4.0-3.6 (6 H, m), 3.2-2.9 (5 H, m), 2.8 (2 H, m), 1.81 (1 H, m), 1.78-1.44 (10 H, m), 1.35 (4 H, m), 0.95 (24 H, m).

Example G39

Compound 41: Compound 40 (82 mg, 0.1 mmol) and L-alanine isopropyl ester hydrochloride (92 mg, 0.53 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in pyridine (1 mL) and diisopropylethylamine (136 μL, 0.78 mmol) was added. To above mixture was added a solution of Aldrithiol (72 mg, 0.33 mmol) and triphenylphosphine (87 mg, 0.33 mmol) in pyridine (1 mL). The reaction mixture was stirred at 75°C for 20 hrs, and solvents were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with water (2x), and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave an oil, which was purified by flash column chromatography (CH_2Cl_2/MeOH = 100/1 to100/3) to afford compound 41 (19 mg): ^1H NMR ($CDCl_3$) δ 7.71 (2 H, d, J = 8.9 Hz), 7.2-7.35 (5 H, m), 7.15 (2 H, m), 7.01 (2 H, d, J = 8.9 Hz), 6.87 (2 H, m), 5.65 (1 H, d, J = 5.4 Hz), 5.05-4.93 (2 H, m), 4.3 (2 H, m), 4.19 (1 H, m), 3.98 (1 H, m), 3.88 (3 H, s), 3.80 (2 H, m), 3.70 (3 H, m), 3.18 (1 H, m), 2.95 (4 H, m), 2.78 (2 H, m), 1.82 (1 H, m), 1.62 (2 H, m), 1.35 (3 H, m), 1.25-1.17 (6 H, m), 0.93 (3 H, d, J = 6.4 Hz), 0.88 (3 H, d, J = 6.4 Hz).

Example G40

Compound 42: Compound 40 (100 mg, 0.13 mmol) and L-glycine butyl ester hydrochloride (88 mg, 0.53 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in pyridine (1 mL) and diisopropylethylamine (136 μL, 0.78 mmol) was added. To above mixture was added a solution of Aldrithiol (72 mg, 0.33 mmol) and triphenylphosphine (87 mg, 0.33 mmol) in pyridine (1 mL). The reaction mixture was stirred at 75°C for 20 hrs, and solvents were evaporated under reduced pressure. The mixture was diluted with ethyl acetate,

and was washed with water (2x), and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave an oil, which was purified by flash column chromatography (CH_2Cl_2/MeOH = 100/1 to100/3) to afford compound 42 (18 mg): ^1H NMR ($CDCl_3$) δ 7.71 (2 H, d, J = 9.2 Hz), 7.35-7.24 (5 H, m), 7.14 (2 H, m), 7.00 (2 H, d, J = 8.8 Hz), 6.87 (2 H, m), 5.65 (1 H, d, J = 5.2 Hz), 5.04 (1 H, m), 4.92 (1 H, m), 4.36 (2 H, m), 4.08 (2 H, m), 3.95 (3 H, m), 3.88 (3 H, s), 3.80 (2 H, m), 3.76 (3 H, m), 3.54 (1 H, m), 3.15 (1 H, m), 2.97 (4 H, m), 2.80 (2 H, m), 1.82 (1 H, m), 1.62 (4 H, m), 1.35 (2 H, m), 0.9 (9 H, m).

Example Section H

Example H1

Sulfonamide 1: To a suspension of epoxide (20 g, 54.13 mmol) in 2-propanol (250 mL) was added isobutylamine (54 mL, 541 mmol) and the solution was refluxed for 30 min. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH_2Cl_2 (250 mL) and cooled to 0°C. Triethylamine (15.1 mL, 108.26 mmol) was added followed by the addition of 4-nitrobenzenesulfonyl chloride (12 g, 54.13 mmol) and the solution was stirred for 40 min at 0°C, warmed to room temperature for 2 h, and evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was recrystallized from EtOAc/hexane to give the sulfonamide (30.59 g, 90%) as an off-white solid.

Example H2

Phenol 2: A solution of sulfonamide 1 (15.58 g, 24.82 mmol) in EtOH (450 mL) and CH_2Cl_2 (60 mL) was treated with 10% Pd/C (6 g). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 24 h. The reaction mixture was filtered through a plug of celite and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (6% MeOH/CH_2Cl_2) to give the phenol (11.34 g, 90%) as a white solid.

Example H3

Dibenzylphosphonate 3: To a solution of phenol 2 (18.25 g, 35.95 mmol) in CH_3CN (200 mL) was added Cs_2CO_3 (23.43 g, 71.90 mmol) and triflate (19.83 g, 46.74 mmol). The reaction mixture was stirred at room temperature for 1 h and the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (2/1-EtOAc/hexane) to give the dibenzylphosphonate (16.87 g, 60%) as a white solid.

Example H4

Amine 4: A solution of dibenzylphosphonate (16.87 g, 21.56 mmol) in CH_2Cl_2 (60 mL) at 0°C was treated with trifluoroacetic acid (30 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. Volatiles were evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5 N NaOH (2x), water (2x), saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure to give the amine (12.94 g, 88%) as a white solid.

Example H5

Carbonate 5: To a solution of (S)-(+)-3-hydroxytetrahydrofuran (5.00 g, 56.75 mmol) in CH_2Cl_2 (80 mL) was added triethylamine (11.86 mL, 85.12 mmol) and bis(4-nitrophenyl)carbonate (25.90 g, 85.12 mmol). The reaction mixture was stirred at room temperature for 24 h and partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The CH_2Cl_2 layer was dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (2/1-EtOAc/hexane) to give the carbonate (8.62 g, 60%) as a pale yellow oil which solidified upon refrigerating.

Example H6

Carbamate 6: Two methods have been used.

Method 1: To a solution of 4 (6.8 g, 9.97 mmol) and 5 (2.65 g, 10.47 mmol) in CH_3CN (70 mL) at 0 °C was added 4-(dimethylamino)pyridine (2.44 g, 19.95 mmol). The reaction mixture was stirred at 0°C for 3 h and concentrated. The residue was dissolved in EtOAc and washed with 0.5 N NaOH, saturated $NaHCO_3$, H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the carbamate (3.97 g, 50%) as a pale yellow solid.

Method 2: To a solution of 4 (6.0 g, 8.80 mmol) and 5 (2.34 g, 9.24 mmol) in CH_3CN (60 mL) at 0°C was added 4-(dimethylamino)pyridine (0.22 g, 1.76 mmol) and N, N-diisopropylethylamine (3.07 mL, 17.60 mmol). The reaction mixture was stirred at 0°C for 1 h and warmed to room temperature overnight. The solvent was evaporated under reduced pressure. The crude product was dissolved in EtOAc and washed with 0.5 N NaOH, saturated $NaHCO_3$, H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified

by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the carbamate (3.85 g, 55%) as a pale yellow solid.

Example H7

Phosphonic Acid 7: To a solution of 6 (7.52 g, 9.45 mmol) in MeOH (350 mL) was added 10% Pd/C (3 g). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 48 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (5.24 g, 90%) as a white solid.

Example H8

Cbz Amide 8: To a solution of 7 (5.23 g, 8.50 mmol) in CH_3CN (50 mL) was added N, O-bis(trimethylsilyl)acetamide (16.54 mL, 68 mmol) and then heated to 70°C for 3 h. The reaction mixture was cooled to room temperature and concentrated. The residue was co-evaporated with toluene and dried under vacuum to afford the silylated intermediate which was used directly without any further purification. To a solution of the silylated intermediate in CH_2Cl_2 (40 mL) at 0°C was added pyridine (1.72 mL, 21.25 mmol) and benzyl chloroformate (1.33 mL, 9.35 mmol). The reaction mixture was stirred at 0°C for 1 h and warmed to room temperature overnight. A solution of MeOH (50 mL) and 1% aqueous HCl (150 mL) was added at 0°C and stirred for 30 min. CH_2Cl_2 was added and two layers were separated. The organic layer was dried with Na_2SO_4, filtered, concentrated, co-evaporated with toluene, and dried under vacuum to give the Cbz amide (4.46 g, 70%) as an off-white solid.

Example H9

Diphenylphosphonate 9: A solution of 8 (4.454 g, 5.94 mmol) and phenol (5.591 g, 59.4 mmol) in pyridine (40 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (4.903 g, 23.76 mmol) was added. The reaction mixture was stirred at 70°C for 4 h and cooled to room temperature. EtOAc was added and the side product 1,3-dicyclohexyl urea was filtered off. The filtrate was concentrated and dissolved in CH_3CN (20 mL) at 0°C. The mixture was treated with DOWEX 50W x 8-400 ion-exchange resin and stirred for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated. The crude product was purified by column chromatography on silica gel (4% 2-propanol/CH_2Cl_2) to give the diphenylphosphonate (2.947 g, 55%) as a white solid.

Example H10

Monophosphonic Acid 10: To a solution of 9 (2.945 g, 3.27 mmol) in CH_3CN (25 mL) at 0°C was added 1N NaOH (8.2 mL, 8.2 mmol). The reaction mixture was stirred at 0°C for 1 h. DOWEX 50W x 8-400 ion-exchange resin was added and the reaction mixture was stirred for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated and co-evaporated with toluene. The crude product was triturated with EtOAc/hexane (1/2) to give the monophosphonic acid (2.427 g, 90%) as a white solid.

Example H11

Cbz Protected Monophosphoamidate 11: A solution of 10 (2.421 g, 2.93 mmol) and L-alanine isopropyl ester hydrochloride (1.969 g, 11.73 mmol) in pyridine (20 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (3.629 g, 17.58 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. The solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl, H_2O, saturated $NaHCO_3$, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4% 2-propanol/CH_2Cl_2) to give the monoamidate (1.569 g, 57%) as a white solid.

Example H12

Monophosphoamidate12: To a solution of 11 (1.569 g, 1.67 mmol) in EtOAc (80 mL) was added 10% Pd/C (0.47 g). The suspension was stirred under H_2 atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and the crude product was purified by column chromatography on silica gel (CH_2Cl_2 to 1-8% 2-propanol/CH_2Cl_2) to give the monophosphoamidate 12a (1.12 g, 83%, **GS 108577**, 1:1 diastereomeric mixture A/B) as a white solid: ^1H NMR ($CDCl_3$) δ 7.45 (dd, 2H), 7.41-7.17 (m, 7H), 6.88 (dd, 2H), 6.67 (d, J = 8.4 Hz, 2H), 5.16 (broad s, 1H), 4.95 (m, 1H), 4.37-4.22 (m, 5H), 3.82-3.67 (m, 7H), 2.99-2.70 (m, 6H), 2.11-1.69 (m, 3H), 1.38 (m, 3H), 1.19 (m, 6H), 0.92 (d, J = 6.3 Hz, 3H), 0.86 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.5, 19.6. 12b (29 mg, 2%, **GS108578**, diastereomer A) as a white solid: ^1H NMR ($CDCl_3$) δ 7.43 (d, J = 7.8 Hz, 2H), 7.35-7.17 (m, 7H), 6.89 (d, J = 8.4 Hz, 2H), 6.67 (d, J = 8.4 Hz, 2H), 5.16 (broad s, 1H), 4.96 (m, 1H), 4.38-4.32 (m, 4H), 4.20 (m, 1H), 3.82-3.69 (m, 7H), 2.99-2.61 (m, 6H), 2.10 (m, 1H), 1.98 (m, 1H), 1.80 (m, 1H), 1.38 (d, J = 7.2 Hz, 3H), 1.20 (d, J = 6.3 Hz, 6H), 0.92 (d, J

= 6.3 Hz, 3H), 0.86 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.5. 12c (22 mg, 1.6%, **GS 108579**, diastereomer B) as a white solid : ^{1}H NMR ($CDCl_3$) δ 7.45 (d, J = 8.1 Hz, 2H), 7.36-7.20 (m, 7H), 6.87 (d, J = 8.7 Hz, 2H), 6.67 (d, J = 8.4 Hz, 2H), 5.15 (broad s, 1H), 4.95 (m, 1H), 4.34-4.22 (m, 5H), 3.83-3.67 (m, 7H), 2.99-2.64 (m, 6H), 2.11-1.68 (m, 3H), 1.33 (d, J = 6.9 Hz, 3H), 1.20 (d, J = 6.0 Hz, 6H), 0.92 (d, J = 6.3 Hz, 3H), 0.86 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 19.6.

Example H13

Sulfonamide 13: To a suspension of epoxide (1.67 g, 4.52 mmol) in 2-propanol (25 mL) was added isobutylamine (4.5 mL, 45.2 mmol) and the solution was refluxed for 30 min. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH_2Cl_2 (20 mL) and cooled to 0°C. Triethylamine (1.26 mL, 9.04 mmol) was added followed by the treatment of 3-nitrobenzenesulfonyl chloride (1.00 g, 4.52 mmol). The solution was stirred for 40 min at 0°C, warmed to room temperature for 2 h, and evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (1/1-EtOAc/hexane) to give the sulfonamide (1.99 g, 70%) as a white solid.

Example H14

Phenol 14: Sulfonamide 13 (1.50 g, 2.39 mmol) was suspended in HOAc (40 mL) and concentrated HCl (20 mL) and heated to reflux for 3 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was partitioned between 10% MeOH/CH_2Cl_2 and saturated $NaHCO_3$. The organic layers were washed with $NaHCO_3$, H_2O, dried with Na_2SO_4, filtered, and concentrated to give a yellow solid. The crude product was dissolved in $CHCl_3$ (20 mL) and treated with triethylamine (0.9 mL, 6.45 mmol) followed by the addition of Boc_2O (0.61 g, 2.79 mmol). The reaction mixture was stirred at room temperature for 6 h. The product was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ layer was washed with $NaHCO_3$, H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (1-5% MeOH/CH_2Cl_2) to give the phenol (0.52 g, 45%) as a pale yellow solid.

Example H15

Dibenzylphosphonate 15: To a solution of phenol 14 (0.51 g, 0.95 mmol) in CH_3CN (8 mL) was added Cs_2CO_3 (0.77 g, 2.37 mmol) and triflate (0.8 g, 1.90 mmol). The reaction mixture was stirred at room temperature for 1.5 h and the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% MeOH/CH_2Cl_2) to give the dibenzylphosphonate (0.62 g, 80%) as a white solid.

Example H16

Amine 16: A solution of dibenzylphosphonate 15 (0.61 g, 0.75 mmol) in CH_2Cl_2 (8 mL) at 0°C was treated with trifluoroacetic acid (2 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. Volatiles were evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5 N NaOH (2x), water (2x), saturated NaCl, dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give the amine (0.48 g, 90%) which was used directly without any further purification.

Example H17

Carbamate 17: To a solution of amine 16 (0.48 g, 0.67 mmol) in CH_3CN (8 mL) at 0°C was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (0.2 g, 0.67 mmol, prepared according to Ghosh *et al.*, *J. Med. Chem.* 1996, *39*, 3278.) and 4-(dimethylamino)pyridine (0.17 g, 1.34 mmol). After stirring for 2 h at 0°C, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5N NaOH (2 x), 5% citric acid (2 x), saturated $NaHCO_3$, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the carbamate (0.234 g, 40%) as a white solid.

Example H18

Analine 18: To a solution of carbamate 17 (78 mg, 0.09 mmol) in 2 mL HOAc was added zinc powder. The reaction mixture was stirred at room temperature for 1.5 h and filtered

through a small plug of celite. The filtrate was concentrated and co-evaporated with toluene. The crude product was purified by column chromatography on silica gel (5% 2-propanaol/CH_2Cl_2) to give the analine (50 mg, 66%) as a white solid.

Example H19

Phosphonic Acid 19: To a solution of analine (28 mg, 0.033mmol) in MeOH (1 mL) and HOAc (0.5 mL) was added 10% Pd/C (14 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 6 h. The reaction mixture was filtered through a small plug of celite. The filtrate was concentrated, co-evaporated with toluene, and dried under vacuum to give the phosphonic acid (15 mg, 68%, **GS 17424**) as a white solid: ^1H NMR (DMSO-d_6) δ 7.16-6.82 (m, 8H), 5.50 (d, 1H), 4.84 (m, 1H), 3.86-3.37 (m, 9H), 2.95-2.40 (m, 6H), 1.98 (m, 1H), 1.42-1.23 (m, 2H), 0.84 (d, J = 6.3 Hz, 3H), 0.79 (d, J = 6.3 Hz,3H). MS (ESI) 657 (M-H).

Example H20

Phenol 21: A suspension of aminohydrobromide salt 20 (22.75 g, 44 mmol) in CH_2Cl_2 (200 mL) at 0°C was treated with triethylamine (24.6 mL, 176 mmol) followed by slow addition of chlorotrimethylsilane (11.1 mL, 88 mmol). The reaction mixture was stirred at 0°C for 30 min and warmed to room temperature for 1 h. The solvent was removed under reduced pressure to give a yellow solid. The crude product was dissolved in CH_2Cl_2 (300 mL) and treated with triethylamine (18.4 mL, 132 mmol) and Boc_2O (12 g, 55 mmol). The reaction mixture was stirred at room temperature overnight. The product was partitioned between CH_2Cl_2 and H_2O. The CH_2Cl_2 layer was washed with $NaHCO_3$, H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was dissolved in THF (200 mL) and treated with 1.0 M TBAF (102 mL, 102 mmol) and HOAc (13 mL). The reaction mixture was stirred at room temperature for 1 h and concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 and H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (1-3% 2-propanol/CH_2Cl_2) to give the phenol (13.75 g, 58%) as a white solid.

Example H21

Dibenzylphosphonate 22: To a solution of phenol 21 (13.70 g, 25.48 mmol) in THF (200 mL) was added Cs_2CO_3 (16.61 g, 56.96 mmol) and triflate (16.22 g, 38.22 mmol). The reaction

mixture was stirred at room temperature for 1 h and the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% MeOH/CH_2Cl_2) to give the dibenzylphosphonate (17.59 g, 85%) as a white solid.

Example H22

Amine 23: A solution of dibenzylphosphonate 22 (17.58 g, 21.65 mmol) in CH_2Cl_2 (60 mL) at 0°C was treated with trifluoroacetic acid (30 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 1.5 h. Volatiles were evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5 N NaOH (2x), water (2x), saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure to give the amine (14.64 g, 95%) which was used directly without any further purification.

Example H23

Carbamate 24: To a solution of amine 23 (14.64 g, 20.57 mmol) in CH_3CN (200 mL) at 0°C was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (6.07 g, 20.57 mmol, prepared according to Ghosh *et al.*, *J. Med. Chem.* 1996, 39, 3278.) and 4-(dimethylamino)pyridine (5.03 g, 41.14mmol). After stirring for 2 h at 0°C, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5N NaOH (2 x), 5% citric acid (2 x), saturated $NaHCO_3$, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the carbamate (10 g, 56%) as a white solid.

Example H24

Phosphonic Acid 25: To a solution of carbamate 24 (8 g, 9.22 mmol) in EtOH (500 mL was added 10% Pd/C (4 g). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 30 h. The reaction mixture was filtered through a plug of celite. The celite paste was suspended in pyridine and stirred for 30 min and filtered. This process was repeated twice.

The combined solution was concentrated under reduced pressure to give the phosphonic acid (5.46 g, 90%) as an off-white solid.

Example H25

Cbz Amide 26: To a solution of 25 (5.26 g, 7.99 mmol) in CH_3CN (50 mL) was added N, O-bis(trimethylsilyl)acetamide (15.6 mL, 63.92 mmol) and then heated to 70°C for 3 h. The reaction mixture was cooled to room temperature and concentrated. The residue was co-evaporated with toluene and dried under vacuum to afford the silylated intermediate which was used directly without any further purification. To a solution of the silylated intermediate in CH_2Cl_2 (40 mL) at 0°C was added pyridine (1.49 mL, 18.38 mmol) and benzyl chloroformate (1.25mL, 8.79 mmol). The reaction mixture was stirred at 0°C for 1 h and warmed to room temperature overnight. A solution of MeOH (50 mL) and 1% aqueous HCl (150 mL) was added at 0°C and stirred for 30 min. CH_2Cl_2 was added and two layers were separated. The organic layer was dried with Na_2SO_4, filtered, concentrated, co-evaporated with toluene, and dried under vacuum to give the Cbz amide (4.43 g, 70%) as an off-white solid.

Example H26

Diphenylphosphonate 27: A solution of 26 (4.43 g, 5.59 mmol) and phenol (4.21 g, 44.72 mmol) in pyridine (40 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (4.62 g, 22.36 mmol) was added. The reaction mixture was stirred at 70°C for 36 h and cooled to room temperature. EtOAc was added and the side product 1,3-dicyclohexyl urea was filtered off. The filtrate was concentrated and dissolved in CH_3CN (20 mL) at 0°C. The mixture was treated with DOWEX 50W x 8-400 ion-exchange resin and stirred for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated. The crude product was purified by column chromatography on silica gel (2/1-EtOAc/hexane to EtOAc) to give the diphenylphosphonate (2.11 g, 40%) as a pale yellow solid.

Example H27

Monophosphonic Acid 28: To a solution of 27 (2.11 g, 2.24 mmol) in CH_3CN (15 mL) at 0°C was added 1N NaOH (5.59 mL, 5.59 mmol). The reaction mixture was stirred at 0°C for 1 h. DOWEX 50W x 8-400 ion-exchange resin was added and the reaction mixture was stirred for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated and co-evaporated

with toluene. The crude product was triturated with EtOAc/hexane (1/2) to give the monophosphonic acid (1.75 g, 90%) as a white solid.

Example H28

Cbz Protected Monophosphoamidate 29: A solution of 28 (1.54 g, 1.77 mmol) and L-alanine isopropyl ester hydrochloride (2.38 g, 14.16 mmol) in pyridine (15 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (2.20 g, 10.62 mmol) was added. The reaction mixture was stirred at 70°C overnight and cooled to room temperature. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl, H_2O, saturated $NaHCO_3$, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% $MeOH/CH_2Cl_2$) to give the monophosphoamidate (0.70g, 40%) as an off-white solid.

Example H29

Monophosphoamidate 30a-b: To a solution of 29 (0.70 g, 0.71 mmol) in EtOH (10 mL) was added 10% Pd/C (0.3 g). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 6 h. The reaction mixture was filtered through a small plug of celite. The filtrate was concentrated and the crude products were purified by column chromatography on silica gel (7-10% $MeOH/CH_2Cl_2$) to give the monoamidates 30a (0.106 g, 18%, **GS 77369**, 1/1 diastereomeric mixture) as a white solid: ^1H NMR ($CDCl_3$) δ 7.71 (d, J = 8.7 Hz, 2H), 7.73-7.16 (m, 5H), 7.10-6.98 9m, 4H), 6.61 (d, J = 8.1 Hz, 2H), 5.67 (d, J = 4.8 Hz, 1H), 5.31-4.91 (m, 2H), 4.44 (m, 2H), 4.20 (m, 1H), 4.00-3.61 (m, 6H), 3.18-2.74 (m, 7H), 1.86-1.64 (m, 3H), 1.38 (m, 3H), 1.20 (m, 6H), 0.93 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 19.1, 18; MS(ESI) 869 (M+Na). 30b (0.200 g, 33%, **GS 77425**, 1/1 diastereomeric mixture) as a white solid: ^1H NMR ($CDCl_3$) δ 7.73 (dd, J = 8.7 Hz, J = 1.5 Hz, 2H), 7.36-7.16 (m, 5H), 7.09-7.00 (m, 4H), 6.53 (d, J = 8.7 Hz, 2H), 5.66 (d, J = 5.4 Hz, 1H), 5.06-4.91 (m, 2H), 4.40 (m, 2H), 4.20 (m, 1H), 4.00-3.60 (m, 6H), 3.14 (m, 3H), 3.00-2.65 (m, 6H), 1.86-1.60 (m, 3H), 1.35 (m, 3H), 1.20 (m, 9H), 0.92 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 19.0, 17.9. MS (ESI) 897 (M+Na).

Example H30

Synthesis of Bisamidates 32: A solution of phosphonic acid 31 (100 mg, 0.15 mmol) and L-valine ethyl ester hydrochloride (108 mg, 0.60 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph_3P (117 mg, 0.45 mmol) and 2,2'-dipyridyl disulfide (98 mg, 0.45 mmol) in pyridine (1 mL) followed by addition of N,N-diisopropylethylamine (0.1 mL, 0.60 mmol). The reaction mixture was stirred at room temperature for two days. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel to give the bisamidate (73 mg, 53%, **GS 17389**) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.1 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.1 Hz, 2H), 5.66 (d, J = 4.8 Hz, 1H), 5.05 (m, 1H), 4.95 (d, J = 8.7 Hz, 1H), 4.23-4.00 (m ,4H,), 3.97-3.68 (m, 11H), 3.39-2.77 (m, 9H), 2.16 (m, 2H), 1.82-1.60 (m, 3H), 1.31-1.18 (m, 6H), 1.01-0.87 (m, 18H); ^{31}P NMR ($CDCl_3$) δ 21.3; MS (ESI) 950 (M+Na).

Example H31

Triflate 34: To a solution of phenol 33 (2.00 g, 3.46 mmol) in THF (15 mL) and CH_2Cl_2 (5 mL) was added N-phenyltrifluoromethanesulfonimide (1.40 g, 3.92 mmol) and cesium carbonate (1.40 g, 3.92 mmol). The reaction mixture was stirred at room temperature overnight and concentrated. The crude product was partitioned between CH_2Cl_2 and saturated NaCl, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% MeOH/CH_2Cl_2) to give the triflate (2.09 g, 85%) as a white solid.

Example H32

Aldehyde 35: To a suspension of triflate 34 (1.45 g, 2.05 mmol), palladium (II) acetate (46 mg, 0.20 mmol) and 1,3-bis(diphenylphosphino)propane (84 mg, 0.2 mmol) in DMF (8 mL) under CO atmosphere (balloon) was slowly added triethylamine (1.65 mL, 11.87 mmol) and triethylsilane (1.90 mL, 11.87 mmol). The reaction mixture was heated to 70°C under CO atmosphere (balloon) and stirred overnight. The solvent was concentrated under reduced pressure and partitioned between CH_2Cl_2 and H_2O. The organic phase was dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4% 2-propanol/CH_2Cl_2) to give the aldehyde (0.80 g, 66%) as a white solid.

Example H33

Substituted Benzyl Alcohol 36: To a solution of aldehyde 35 (0.80g, 1.35 mmol) in THF (9 mL) and H_2O (1 mL) at –10°C was added $NaBH_4$ (0.13 g, 3.39 mmol). The reaction mixture was stirred for 1 h at –10°C and the solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with $NaHSO_4$, H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (6% 2-propanol/CH_2Cl_2) to give the alcohol (0.56 g, 70%) as a white solid.

Example H34

Substituted Benzyl Bromide 37: To a solution of alcohol 36 (77 mg, 0.13 mmol) in THF (1 mL) and CH_2Cl_2 (1 mL) at 0°C was added triethylamine (0.027 mL, 0.20 mmol) and methanesulfonyl chloride (0.011 mL, 0.14 mmol). The reaction mixture was stirred at 0°C for 30 min and warmed to room temperature for 3 h. Lithium bromide (60 mg, 0.69 mmol) was added and stirred for 45 min. The reaction mixture was concentrated and the residue was partitioned between CH_2Cl_2 and H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (2% MeOH/CH_2Cl_2) to give the bromide (60 mg, 70%).

Example H35

Diethylphosphonate 38: A solution of bromide 37 (49 mg, 0.075 mmol) and triethylphosphite (0.13 mL, 0.75 mmol) in toluene (1.5 mL) was heated to 120°C and stirred overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (6% MeOH/CH_2Cl_2) to give the diethylphosphonate (35 mg, 66%, **GS 191338**) as a white solid: ^1H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.27-7.16 (m, 4H), 7.00 (d, J = 8.7 Hz, 2H), 5.66 (d, J = 5.1 Hz, 1H), 5.00 (m, 2H), 4.04-3.73 (m, 13H), 3.13-2.80 (m, 9H), 1.82-1.64 (m, 3H), 1.25 (t, J = 6.9 Hz, 6H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 26.4; MS (ESI) 735 (M+Na).

Example H36

N-tert-Butoxycarbonyl-O-benzyl-L-serine 39: To a solution of Boc-L-serine (15 g, 73.09 mmol) in DMF (300 mL) at 0°C was added NaH (6.43 g, 160.80 mmol, 60% in mineral oil) and stirred for 1.5 h at 0°C. After the addition of benzyl bromide (13.75 g, 80.40 mmol), the

reaction mixture was warmed to room temperature and stirred overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in H_2O. The crude product was partitioned between H_2O and Et_2O. The aqueous phase was acidified to pH<4 with 3 N HCl and extracted with EtOAc three times. The combined EtOAc solution was washed with H_2O, dried with Na_2SO_4, filtered, and concentrated to give the N-tert-butoxycarbonyl-O-benzyl-L-serine (17.27 g, 80%).

Example H37

Diazo Ketone 40: To a solution of N-tert-Butoxycarbonyl-O-benzyl-L-serine 39 (10 g, 33.86 mmol) in dry THF (120 mL) at –15°C was added 4-methylmorpholine (3.8 mL, 34.54 mmol) followed by the slow addition of isobutylchloroformate (4.40 mL, 33.86 mmol). The reaction mixture was stirred for 30 min and diazomethane (~50 mmol, generated from 15 g Diazald according to *Aldrichimica Acta* 1983, 16, 3) in ether (~150 mL) was poured into the mixed anhydride solution. The reaction was stirred for 15 min and was then placed in an ice bath at 0°C and stirred for 1 h. The reaction was allowed to warm to room temperature and stirred overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in EtOAc, washed with water, saturated $NaHCO_3$, saturated NaCl, dried with Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography (EtOAc/hexane) to afford the diazo ketone (7.50 g, 69%) as a yellow oil.

Example H38

Chloroketone 41: To a suspension of diazoketone 40 (7.50 g, 23.48 mmol) in ether (160 mL) at 0°C was added 4N HCl in dioxane (5.87 mL, 23.48 mmol). The reaction mixture was stirred at 0°C for 1 h. The reaction solvent was evaporated under reduced pressure to give the chloroketone which was used directly without any further purification.

Example H39

Chloroalcohol 42: To a solution of chloroketone 41 (7.70 g, 23.48 mmol) in THF (90 mL) was added water (10 mL) and the solution was cooled to 0°C. A solution of $NaBH_4$ (2.67 g, 70.45 mmol) in water (4 mL) was added dropwise over a period of 10 min. The mixture was stirred for 1 h at 0°C and saturated $KHSO_4$ was slowly added until the pH<4 followed by saturated NaCl. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered,

and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (1/4 EtOAc/hexane) to give the chloroalcohol (6.20 g, 80%) as a diastereomeric mixture.

Example H40

Epoxide 43: A solution of chloroalcohol 42 (6.20 g, 18.79 mmol) in EtOH (150 mL) was treated with 0.71 M KOH (1.27 g, 22.55 mmol) and the mixture was stirred at room temperature for 1 h. The reaction mixture was evaporated under reduced pressure and the residue was partitioned between EtOAc and water. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (1/6 EtOAc/hexane) to afford the desired epoxide 43 (2.79 g, 45%) and a mixture of diastereomers 44 (1.43 g, 23%).

Example H41

Sulfonamide 45: To a suspension of epoxide 43 (2.79 g, 8.46 mmol) in 2-propanol (30 mL) was added isobutylamine (8.40 mL, 84.60 mmol) and the solution was refluxed for 1 h. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH_2Cl_2 (40 mL) and cooled to 0°C. Triethylamine (2.36 mL, 16.92 mmol) was added followed by the addition of 4-methoxybenzenesulfonyl chloride (1.75 g, 8.46 mmol). The solution was stirred for 40 min at 0°C, warmed to room temperature, and evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was directly used without any further purification.

Example H42

Silyl Ether 46: A solution of sulfonamide 45 (5.10 g, 8.46 mmol) in CH_2Cl_2 (50 mL) was treated with triethylamine (4.7 mL, 33.82 mmol) and TMSOTf (3.88 mL, 16.91 mmol). The reaction mixture was stirred at room temperature for 1 h and partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic extracts were washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (1/6 EtOAc/hexane) to give the silyl ether (4.50 g, 84%) as a thick oil.

Example H43

Alcohol 47: To a solution of silyl ether 46 (4.5 g, 7.14 mmol) in MeOH (50 mL) was added 10% Pd/C (0.5 g). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 2 h. The reaction mixture was filtered through a plug of celite and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% MeOH/CH_2Cl_2) to give the alcohol (3.40 g, 85%) as a white solid.

Example H44

Aldehyde 48: To a solution of alcohol 47 (0.60 g, 1.07 mmol) in CH_2Cl_2 (6 mL) at 0°C was added Dess Martin reagent (0.77 g, 1.82 mmol). The reaction mixture was stirred at 0°C for 3 h and partitioned between CH_2Cl_2 and $NaHCO_3$. The organic phase was washed with H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (1/4 EtOAc/hexane) to give the aldehyde (0.45 g, 75%) as a pale yellow solid.

Example H45

Sulfonamide 50: To a suspension of epoxide (2.00 g, 5.41 mmol) in 2-propanol (20 mL) was added amine 49 (4.03 g, 16.23 mmol) (prepared in 3 steps starting from 4-(aminomethyl)piperidine according to *Bioorg. Med. Chem. Lett.*, 2001, 11, 1261.). The reaction mixture was heated to 80°C and stirred for 1 h. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH_2Cl_2 (20 mL) and cooled to 0°C. Triethylamine (4.53 mL, 32.46 mmol) was added followed by the addition of 4-methoxybenzenesulfonyl chloride (3.36 g, 16.23 mmol). The solution was stirred for 40 min at 0°C, warmed to room temperature for 1.5 h, and evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the sulfonamide (2.50 g, 59%).

Example H46

Amine 51: A solution of sulfonamide 50 (2.50 g, 3.17 mmol) in CH_2Cl_2 (6 mL) at 0°C was treated with trifluoroacetic acid (3 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 1.5 h. Volatiles were evaporated under reduced

pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5 N NaOH (2x), water (2x) and saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure to give the amine (1.96 g, 90%) which was used directly without any further purification.

Example H47

Carbamate 52: To a solution of amine 51 (1.96 g, 2.85 mmol) in CH_3CN (15mL) at 0°C was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (0.84g, 2.85mmol, prepared according to Ghosh *et al.*, *J. Med. Chem.* 1996, 39, 3278.) and 4-(dimethylamino)pyridine (0.70 g, 5.70 mmol). After stirring for 2 h at 0°C, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5N NaOH (2 x), 5% citric acid (2 x), saturated $NaHCO_3$, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the carbamate (1.44 g, 60%) as a white solid.

Example Section I

Example I1

Carbonate 2: To a solution of (R)-(+)-3-hydroxytetrahydrofuran (1.23 g, 14 mmol) in CH_2Cl_2 (50 mL) was added triethylamine (2.9 mL, 21 mmol) and bis(4-nitrophenyl)carbonate (4.7 g, 15.4 mmol). The reaction mixture was stirred at room temperature for 24 h and partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The CH_2Cl_2 layer was dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (2/1-EtOAc/hexane) to give the carbonate (2.3 g, 65%) as a pale yellow oil which solidified upon standing.

Example I2

Carbamate 3: To a solution of 1 (0.385 g, 0.75 mmol) and 2 (0.210 g, 0.83 mmol) in CH_3CN (7 mL) at room temperature was added N, N-diisopropylethylamine (0.16 mL, 0.90 mmol). The reaction mixture was stirred at room temperature for 44 h. The solvent was evaporated under reduced pressure. The crude product was dissolved in EtOAc and washed with saturated $NaHCO_3$, brine, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (1/1-EtOAc/hexane) to give the carbamate (0.322 g, 69%) as a white solid: mp 98-100°C (uncorrected).

Example I3

Phenol 4: To a solution of 3 (0.31 g, 0.49 mmol) in EtOH (10 mL) and EtOAc (5 mL) was added 10% Pd/C (30 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 15 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phenol (0.265 g) in quantitative yield.

Example I4

Diethylphosphonate 5: To a solution of phenol 4 (100 mg, 0.19 mmol) in THF (3 mL) was added Cs_2CO_3 (124 mg, 0.38 mmol) and triflate (85 mg, 0.29 mmol). The reaction mixture was stirred at room temperature for 4 h and the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried

with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (5% 2-propanol/CH_2Cl_2) to give the diethylphosphonate (63 mg, 49%, **GS 16573**) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.65 (d, J = 8.7Hz, 2H), 7.21 (d, J = 8.7 Hz, 2H), 6.95 (d, J = 9 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 5.06 (broad, s, 1H), 4.80 (d, J = 7.5 Hz, 1H), 4.19 (m, 6H), 3.83 (s, 3H), 3.80-3.70 (m, 6H), 3.09-2.72 (m, 6H), 2.00 (m, 1H), 1.79 (m, 2H), 1.32 (t, J = 7.5 Hz, 6H), 0.86 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H); ^{31}P NMR δ 17.8.

Example I5

Dibenzylphosphonate 6: To a solution of phenol 4 (100 mg, 0.19 mmol) in THF (3 mL) was added Cs_2CO_3 (137 mg, 0.42 mmol) and triflate (165 mg, 0.39 mmol). The reaction mixture was stirred at room temperature for 6 h and the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (5% 2-propanol/CH_2Cl_2) to give the dibenzylphosphonate (130 mg, 84%, **GS 16574**) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.65 (d, J = 9 Hz, 2H), 7.30 (m, 10H), 7.08 (d, J = 8.4Hz, 2H), 6.94 (d, J = 9 Hz, 2H), 6.77 (d, J = 8.7 Hz, 2H), 5.16-5.04 (m, 5H), 4.80 (d, J = 8.1 Hz, 1H), 4.16 (d, J = 10.2 Hz, 2H), 3.82 (s, 3H), 3.75-3.71 (m, 6H), 3.10-2.72 (m, 6H), 2.00 (m, 1H), 1.79 (m, 2H), 0.86 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H); ^{31} P NMR ($CDCl_3$) δ 18.8.

Example I6

Phosphonic Acid 7: To a solution of 6 (66 mg, 0.08 mmol) in EtOH (3 mL) was added 10% Pd/C (12 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 15 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated under reduced pressure and triturated with EtOAc to give the phosphonic acid (40 mg, 78%, **GS 16575**) as a white solid.

Example I7

Carbonate 8: To a solution of (S)-(+)-3-hydroxytetrahydrofuran (2 g, 22.7 mmol) in CH_3CN (50 mL) was added triethylamine (6.75 mL, 48.4 mmol) and N,N'-disuccinimidyl carbonate (6.4 g, 25 mmol). The reaction mixture was stirred at room temperature for 5 h and

concentrated under reduced pressure. The residue was partitioned between EtOAc and H_2O. The organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc as eluant) followed by recrystallization (EtOAc/hexane) to give the carbonate (2.3 g, 44%) as a white solid.

Example I8

Carbamate 9: To a solution of 1 (0.218 g, 0.42 mmol) and 8 (0.12 g, 0.53 mmol) in CH_3CN (3 mL) at room temperature was added N, N-diisopropylethylamine (0.11 mL, 0.63 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated and the residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic phase was washed with brine, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (1/1-EtOAc/hexane) to give the carbamate (0.176 g, 66%) as a white solid.

Example I9

Phenol 10: To a solution of 9 (0.176 g, 0.28 mmol) in EtOH (10 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 4 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phenol (0.151 g, **GS 10**) in quantitative yield.

Example I10

Diethylphosphonate 11: To a solution of phenol 10 (60 mg, 0.11 mmol) in THF (3 mL) was added Cs_2CO_3 (72 mg, 0.22 mmol) and triflate (66 mg, 0.22 mmol). The reaction mixture was stirred at room temperature for 4 h and the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (5% 2-propanol/CH_2Cl_2) to give the diethylphosphonate (38 mg, 49%, **GS 11**) as a white solid.

Example Section J

Example J1

Triflate 1: To a solution of A (4 g, 6.9 mmol) in THF (30 mL) and CH_2Cl_2 (10 mL) was added Cs_2CO_3 (2.7 g, 8 mmol) and N-phenyltrifluoromethanesulfonimide (2.8 g, 8.0 mmol) and stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure. The residue wsa partitioned between CH_2Cl_2 and saturated brine twice. The organic phase was dried over sodium sulfate and used for next reaction without further purification.

Example J2

Aldehyde 2: A solution of crude above triflate 1 (~6.9 mmol) in DMF (20 mL) was degassed (high vacumn for 5 min, argon purge, repeat 3 times). To this solution were quickly added $Pd(OAc)_2$ (120 mg, 266 μmol) and bis(diphenylphosphino-propane (dppp ,220 mg, 266 μmol), and heated to 70°C. To this reaction mixture was rapidly introduced carbon monoxide, and stirred at room temperature under an atmopheric pressure of carbon monoxide, followed by slow addition of TEA (5.4 mL, 38 mmol) and triethylsilane (3 mL, 18 mmol). The resultant mixture was stirred at 70°C for 16 h, then cooled to room temperature, concentrated under reduced pressure, partitioned between CH_2Cl_2 and saturated brine. The organic phase was concentrated under reduced pressure and purified on silica gel column to afford aldehyde 2 (2.1 g, 51%) as white solid.

Example J3

Compounds 3a-3e: Respresentative Procedure, 3c: A solution of aldehyde 2 (0.35 g, 0.59 mmol), L-alanine isopropyl ester hydrochloride (0.2 g, 1.18 mmol), glacial acetic acid (0.21 g, 3.5 mmol) in 1,2-dichloroethane (10 mL) was stirred at room temperature for 16 h, followed by addition of sodium cyanoborohydride (0.22 g, 3.5 mmol) and methanol (0.5 mL). The resulting solution was stirred at room temperature for one h. The reaction mixture was washed with sodium bicarbonate solution, saturated brine, and chromatographed on silica gel to afford 3c (0.17 g, 40%). ^1H NMR ($CDCl_3$): δ 7.72 (d, 2H), 7.26 (d, 2H), 7.20 (d, 2H), 7.0 (d, 2H), 5.65 (d, 1H), 4.90-5.30 (m, 3H), 3.53-4.0 (m overlapping s, 13H), 3.31 (q, 1H), 2.70-3.20 (m, 7H), 1.50-1.85 (m, 3H), 1.25-1.31 (m, 9H), 0.92 (d, 3H), 0.88 (d, 3H). MS: 706 (M + 1).

Compound	R_1	R_2	Amino Acid
3a	Me	Me	Ala
3b	Me	Et	Ala
3c	Me	iPr	Ala
3d	Me	Bn	Ala
3e	iPr	Et	Val

Example J4

Sulfonamide 1: To a solution of crude amine A (1 g, 3 mmol) in CH_2Cl_2 was added TEA (0.6 g, 5.9 mmol) and 3-methoxybenzenesulfonyl chloride (0.6 g, 3 mmol). The resulting solution was stirred at room temperature for 5 h, and evaporated under reduced pressure. The residue was chromatographed on silica gel to afford sulfonamide 1 (1.0 g, 67%).

Example J5

Amine 2: To a 0°C cold solution of sulfonamide 1 (0.85 g, 1.6 mmol) in CH_2Cl_2 (40 mL) was treated with BBr_3 in CH_2Cl_2 (10 mL of 1 M solution, 10 mmol). The solution was stirred at 0°C 10 min and then warmed to room temperature and stirred for 1.5 h. The reaction mixture was quenched with CH_3OH, concentrated under reduced pressure, azeotroped with CH_3CN three times. The crude amine 2 was used for next reaction without further purification.

Example J6

Carbamate 3: A solution of crude amine 2 (0.83 mmol) in CH_3CN (20 mL) and was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (245 mg, 0.83 mmol, prepared according to Ghosh *et al.*, *J. Med. Chem.* 1996, 39, 3278.) and N,N-dimethylaminopyridine (202 mg, 1.7 mmol). After stirring for 16 h at room temperature, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 and saturated $NaHCO_3$ three times. The organic phase was evaporated under reduced pressure. The residue was purified by chromatography on silica gel affording the carbamate 3 (150 mg, 33%) as a solid.

Example J7

Diethylphosphonate 4: To a solution of carbamate 3(30 mg, 54 μmol) in THF (5 mL) was added Cs_2CO_3 (54 mg, 164 μmol) and triflate # (33 mg, 109 μmol). After stirring the reaction mixture for 30 min at room temperature, additional Cs_2CO_3 (20 mg, 61 μmol) and

triflate (15 mg, 50 μmol) were added and the mixture was stirred for 1 more hour. The reaction mixture was evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 and water. The organic phase was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude product was chromatographed on silica gel and repurified by HPLC (50% CH_3CN-50% H_2O on C18 column) to give the diethylphosphonate 4 (15 mg, 39%). ^1H NMR ($CDCl_3$): δ 7.45 (m, 3H), 7.17-7.30 (m, 6H), 5.64 (d, 1H), 5.10 (d, 1H), 5.02 (q, 1H), 4.36 (d, 2H), 4.18-4.29 (2 q overlap, 4H), 3.60-3.98 (m, 7H), 2.70-3.10 (m, 7H), 1.80-1.90 (m, 1H), 1.44-1.70 (m, 2H + H2O), 1.38 (t, 6H), 0.94 (d, 3H), 0.90 (d, 3H). ^{31}P NMR ($CDCl_3$): 18.7 ppm; MS (ESI) 699 (M + H).

Example J8

Dibenzylphosphonate 5: To a solution of carbamate 3 (100 mg, 182 μmol) in THF (10 mL) was added Cs_2CO_3 (180 mg, 550 μmol) and dibenzylhydroxymethyl phosphonate triflate, Section A, Scheme A2, Compound 9, (150 mg, 360 μmol). After stirring the reaction mixture for 1 h at room temperature, the reaction mixture was evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 and water. The organic phase was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by HPLC (50% CH_3CN-50% H_2O on C18 column) to give the dibenzylphosphonate 5 (110 mg, 72%). ^1H NMR ($CDCl_3$): δ 7.41 (d, 2H), 7.35 (s, 10 H), 7.17-7.30 (m, 6H), 7.09-7.11 (m, 1H), 5.64 (d, 1H), 4.90-5.15 (m, 6H), 4.26 (d, 2H), 3.81-3.95 (m, 4H), 3.64-3.70 (m, 2H), 2.85-3.25 (m, 7H), 1.80-1.95 (m, 1H), 1.35-1.50 (m, 1H), 0.94 (d, 3H), 0.91 (d, 3H). ^{31}P NMR ($CDCl_3$) δ 19.4 ppm; MS (ESI): 845 (M + Na), 1666 (2M + Na).

Example J9

Phosphonic acid 6: A solution of dibenzylphosphonate 5 (85 mg, 0.1 mmol) was dissolved in MeOH (10 mL) treated with 10% Pd/C (40 mg) and stirred under H_2 atmosphere (balloon) overnight. The reaction was purged with N_2, and the catalyst was removed by filtration through celite. The filtrate was evaporated under reduced pressure to afford phosphonic acid 6 (67 mg, quantitatively). ^1H NMR (CD_3OD): δ 7.40-7.55 (m, 3H), 7.10-7.35 (m, 6H), 5.57 (d, 1H), 4.32 (d, 2H), 3.90-3.95 (m, 1H), 3.64-3.78 (m, 5H), 3.47 (m, 1H), 2.85-3.31 (m, 5H), 2.50-

2.60 (m, 1H), 2.00-2.06 (m, 1H), 1.46-1.60 (m, 1H), 1.30-1.34 (m, 1H), 0.9 (d, 3H), 0.90 (d, 3H). ^{31}P NMR (CD_3OD): 16.60 ppm; MS (ESI): 641 (M – H).

Example J10

Sulfonamide 1: To a solution of crude amine A (0.67 g, 2 mmol) in CH_2Cl_2 (50 mL) was added TEA (0.24 g, 24 mmol) and crude 3-acetoxy-4-methoxybenzenesulfonyl chloride (0.58 g, 2.1 mmol, was prepared according to Kratzl *et al.*, *Monatsh. Chem.* 1952, 83, 1042-1043), and the solution was stirred at room temperature for 4 h, and evaporated under reduced pressure. The residue was chromatographed on silica gel to afford sulfonamide 1 (0.64 g, 54%). MS: 587 (M + Na), 1150 (2M + Na)

Phenol 2: Sulfonamide 1 (0.64 g, 1.1 mmol) was treated with saturated NH_3 in MeOH (15 mL) at room temperature for 15 min., then evaporated under reduced pressure. The residue was purified on silica gel column to afford phenol 2 (0.57 g, 96%).

Example J11

Dibenzylphosphonate 3a: To a solution of phenol 2 (0.3 g, 0.57 mmol) in THF (8 mL) was added Cs_2CO_3 (0.55 g, 1.7 mmol)) and dibenzylhydroxymethyl phosphonate triflate (0.5 g, 1.1 mmol). After stirring the reaction mixture for 1 h at room temperature, the reaction mixture was quenched with water and partitioned between CH_2Cl_2 and saturated ammonium chloride aqueous solution. The organic phase was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was chromatographed on silica gel (40% EtOAc/ 60% hexane) to give the dibenzylphosphonate 3a (0.36 g, 82%). ^1H NMR ($CDCl_3$): δ 7.20-7.40 (m, 17H), 6.91 (d, 1H), 5.10-5.25 (2 q(ab) overlap, 4H), 4.58-4.70 (m, 1H), 4.34 (d, 2H), 3.66-3.87 (m + s, 5H), 2.85-3.25 (m, 6H), 1.80-1.95 (m, 1H), 1.58 (s, 9H), 0.86-0.92 (2d, 6H).

Example J12

Diethylphosphonate 3b: To a solution of phenol 2 (0.15 g, 0.28 mmol) in THF (4 mL) was added Cs_2CO_3 (0.3 g, 0.92 mmol)) and diethylhydroxymethyl phosphonate triflate (0.4 g, 1.3 mmol). After stirring the reaction mixture for 1 h at room temperature, the reaction mixture was quenched with water and partitioned between CH_2Cl_2 and saturated $NaHCO_3$ aqueous solution. The organic phase was dried (Na_2SO_4), filtered and evaporated under reduced pressure.

The residue was chromatographed on silica gel (1% CH_3OH-CH_2Cl_2) to give the diethylphosphonate 3b (0.14 g, 73%).

Example J13

Amine 4a: To a solution of 3a (0.35 g, 0.44 mmol) in CH_2Cl_2 (10 mL) was treated with TFA (0.75 g, 6.6 mmol) at room temperature for 2 h. The reaction was evaporated under reduced pressure, azeotroped with CH_3CN twice, dried to afford crude amine 4a. This crude 4a was used for next reaction without further purification.

Example J14

Amine 4b: To a solution of 3b (60 mg, 89 μmol) in CH_2Cl_2 (1 mL) was treated with TFA (0.1 mL, 1.2 mmol) at room temperature for 2 h. The reaction was evaporated under reduced pressure, azeotroped with CH_3CN twice, dried to afford crude amine 4b (68 mg). This crude 4b was used for next reaction without further purification.

Example J15

Carbamate 5a: An ice-cold solution of crude amine 4a (0.44 mmol) in CH_3CN (10 mL) and was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (120 mg, 0.4 mmol) and N,N-dimethylaminopyridine (DMAP, 110 mg, 0.88 mmol). After 4 h, more DMAP (0.55 g, 4.4 mmol) was added to the reaction mixture. After stirring for 1.5 h at room temperature, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was evaporated under reduced pressure. The residue was purified by chromatography on silica gel affording the crude carbamate 5a (220 mg) containing some p-nitrophenol. The crude 5a was repurified by HPLC (50% CH_3CN /50% H_2O) to afford pure carbamate 5a (176 mg, 46%, 2 steps). ^{1}H NMR ($CDCl_3$): δ 7.20-7.36 (m, 1H), 6.94 (d, 1H), 5.64 (d, 1H), 5.10-5.25 (2 q(ab) overlap, 4H), 4.90-5.10 (m, 1H), 4.90 (d, 1H), 4.34 (d, 2H), 3.82-3.91 (m + s, 6H), 3.63-3.70 (m, 3H), 2.79-3.30 (m, 7H), 1.80-1.90 (m, 1H), 1.40-1.50 (m, 1H), 0.94 (d, 3H), 0.89 (d, 3H). ^{31}P NMR ($CDCl_3$): 17.2 ppm.

Example J16

Carbamate 5b: An ice-cold solution of crude amine 4b (89 μmol)) in CH_3CN (5 mL) and was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (26mg,

89 μmol) and N,N-dimethylaminopyridine (DMAP, 22 mg, 0.17 mmol). After 1 h at 0°C, more DMAP (10 mg. 82 μmol) was added to the reaction mixture. After stirring for 2 h at room temperature, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was evaporated under reduced pressure. The residue was purified by HPLC (C18 column, 45% CH_3CN/55% H_2O) to afford pure carbamate 5b (18.8 mg, 29%, 3 steps). ^1H NMR ($CDCl_3$): δ 7.38 (d, 2H), 7.20-7.36 (m, 6H), 7.0 (d, 1H), 5.64 (d, 1H), 4.96-5.03 (m, 2H), 4.39 (d, 2H), 4.20-4.31 (2q overlap, 4H) 3.80-4.00 ((s overlap with m, 7H), 3.60-3.73 (m, 2H), 3.64-3.70 (m, 2H), 2.85-3.30 (m, 7H), 1.80-1.95 (m, 1H), 1.55-1.75 (m, 1H), 1.35-1.50 (s overlap with m, 7H), 0.94 (d, 3H), 0.88 (d, 3H). ^{31}P NMR ($CDCl_3$): 18.1ppm.

Example J17

Phosphonic acid 6: A solution of dibenzylphosphonate 5a (50 mg, 58 μmol) was dissolved in MeOH (5 mL) and EtOAc (3 mL) and treated with 10% Pd/C (25 mg) and was stirred at room temperature under H_2 atmosphere (balloon) for 8 h. The catalyst was filtered off. The filtrate was concentrated and redissolved in MeOH (5 mL), treated with 10% Pd/C (25 mg) and was stirred at room temperature under H_2 atmosphere (balloon) overnight. The catalyst was filtered off. The filtrate was evaporated under reduced pressure to afford phosphonic acid 6 (38 mg, quantitatively). ^1H NMR (CD_3OD): δ 7.42 (m, 1H), 7.36 (s, 1H), 7.10-7.25 (m, 6H), 5.58 7 (d, 1H), 4.32 (d, 2H), 3.90 (s, 3H), 3.60-3.80 (m, 6H), 3.38 (d, 1H), 2.85-3.25 (m, 5H), 2.50-2.60 (m, 1H), 1.95-2.06 (m, 1H), 1.46-1.60 (m, 1H), 1.30-1.40 (m, 1H), 0.93(d, 3H), 0.89 (d, 3H). ^{31}P NMR (CD_3OD): 14.8 ppm; MS (ESI): 671 (M – H).

Example J18

Amine 7: To a 0°C cold solution of diethylphosphonate 3b (80 mg, 0.118 mmol) in CH_2Cl_2 was treated with BBr_3 in CH_2Cl_2 (0.1 mL of 1 M solution, 1 mmol). The solution was stirred at 0°C 10 min and then warmed to room temperature and stirred for 3 h. The reaction mixture was concentrated under reduced pressure. The residue was redissolved in CH_2Cl_2 (containing some CH_3OH, concentrated, azeotroped with CH_3CN three times. The crude amine 7 was used for next reaction without further purification.

Example J19

Carbamate 8: An ice-cold solution of crude amine 7 (0.118 mmol) in CH_3CN (5 mL) and was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (35 mg, 0.118 mmol) and N,N-dimethylaminopyridine (29 mg, 0.24mmol), warmed to room temperature. After stirring for 1 h at room temperature, more DMAP (20 mg, 0.16 mmol) was added to reaction mixture. After 2 h stirred at room temperature, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was evaporated under reduced pressure. The residue was purified by HPLC on C18 (CH_3CN-55%H_2O) to afford the desired carbamate 8 (11.4 mg, 13.4%) as an off-white solid. ^1H NMR ($CDCl_3$): δ 7.20-7.40 (m, 7H), 7.00 (d, 1H), 5.64 (d, 1H), 5.00-5.31 (m, 2H), 4.35 (d, 2H), 4.19-4.30 (2q overlap, 4H), 3.80-4.00 (m, 4H), 3.68-3.74 (m, 2H), 3.08-3.20 (m, 3H), 2.75-3.00 (m, 4H), 1.80-1.90 (m, 1H), 1.55-1.75 (m, 1H), 1.38 (t, 6H), 0.91 (2d overlap, 6H). ^{31}P NMR (CD_3OD): δ 19.5 ppm.

Example Section K

Example K1

Monophenyl-monolactate 3: A mixture of monoacid 1 (0.500 g, 0.7 mmol), alcohol 2 (0.276 g, 2.09 mmol) and dicyclohexylcarbodiimide (0.431 g, 2.09 mmol) in dry pyridine (4 mL) was placed into a 70°C oil bath and heated for two hours. The reaction was monitored by TLC assay (SiO_2, 70% ethyl acetate in hexanes as eluent, product $R_f = 0.68$, visualization by UV). The reaction contents were cooled to ambient temperature with the aid of a cool bath and diluted with dichloromethane (25 mL). TLC assay may show presence of starting material. The diluted reaction mixture was filtered to remove solids. The filtrate was then cooled to 0°C and charged with 0.1 N HCl (10 mL). The pH 4 mixture was stirred for 10 minutes and poured into separatory funnel to allow the layers to separate. The lower organic layer was collected and dried over sodium sulfate. The drying agent was filtered off and the filtrate concentrated to an oil via rotary evaporator (< 30°C warm bath). The crude product oil was purified on pretreated silica gel (deactivated using 10% methanol in dichlorormethane followed by rinse with 60% ethyl acetate in dichloromethane). The product was eluted with 60% ethyl acetate in dichloromethane to afford the product monophenyl-monolactate 3 as a white foam (0.497 g, 86% yield). ^1H NMR ($CDCl_3$) δ 7.75 (d, 2H), 7.40-7.00 (m, 14H), 5.65 (d, 1H), 5.20-4.90 (m, 4H), 4.70 (d, 1H), 4.55-4.50 (m, 1H), 4.00-3.80 (m, 4H), 3.80-3.60 (m, 3H), 3.25-2.75 (m, 7H), 1.50 (d, 3H), 1.30-1.20 (m, 7H), 0.95 (d, 3H), 0.85 (d, 3H). ^{31}P NMR ($CDCl_3$) δ 16.2, 13.9.

Example K2

Monophenyl-monoamidate 5: A mixture of monoacid 1 (0.500 g, 0.70 mmol), amine hydrochloride 4 (0.467 g, 2.78 mmol) and dicyclohexylcarbodiimide (0.862 g, 4.18 mmol) in dry pyridine (8 mL) was placed into a 60°C oil bath, and heated for one hour (at this temperature, product degrades if heating continues beyond this point). The reaction was monitored by TLC assay (SiO_2, 70% ethyl acetate in hexanes as eluent, product $R_f = 0.39$, visualization by UV). The contents were cooled to ambient temperature and diluted with ethyl acetate (15 mL) to precipitate a white solid. The mixture was filtered to remove solids and the filtrate was concentrated via rotary evaporator to an oil. The oil was diluted with dichloromethane (20 mL) and washed with 0.1 N HCl (2 x 20 mL), water (1 x 20 mL) and dilute sodium bicarbonate (1 x

20 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated to an oil via rotary evaporator. The crude product oil was dissolved in dichloromethane (10 mL). Hexane was slowly charged to the stirring solution until cloudiness persisted. The cloudy mixture was stirred for a few mintues until TLC assay showed that the dichloromethane/hexane layer contained no product. The dichloromethane/hexanes layer was decanted and the solid was further purified on silica gel first pretreated with 10% methanol in ethyl acetate and rinsed with 50% ethyl acetate in hexanes. The product 5 was eluted with 50% ethyl acetate in hexanes to afford a white foam (0.255 g, 44% yield) upon removal of solvents. ^{1}H NMR ($CDCl_3$) δ 7.75 (d, 2H), 7.40-7.15 (m, 10H), 7.15-7.00 (t, 2H), 5.65 (d, 1H), 5.10-4.90 (m, 3H), 4.50-4.35 (m, 2H), 4.25-4.10 (m, 1H), 4.00-3.60 (m, 8H), 3.20-2.75 (m, 7H), 1.40-1.20 (m, 11H), 0.95 (d, 3H), 0.85 (d, 3H). ^{31}P NMR ($CDCl_3$) δ 19.1, 18.0.

Example K3

Bisamidate 8: A solution of triphenylphosphine (1.71 g, 6.54 mmol) and aldrithiol (1.44 g, 6.54 mmol) in dry pyridine (5 mL), stirred for at least 20 minutes at room temperature, was charged into a solution of diacid 6 (1.20 g, 1.87 mmol) and amine hydrochloride 7 (1.30 g, 7.47 mmol) in dry pyridine (10 mL). Diisopropylethylamine (0.97 g, 7.48 mmol) was then added to this combined solution and the contents were stirred at room temperature for 20 hours. The reaction was monitored by TLC assay (SiO_2, 5:5:1 ethyl acetate/hexanes/methanol as eluent, product R_f = 0.29, visualization by UV). The reaction mixture was concentrated via rotary evaporator and dissolved in dichloromethane (50 mL). Brine (25 mL) was charged to wash the organic layer. The aqueous layer was back extracted with dichloromethane (1 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated via rotary evaporator to afford an oil. The crude product oil was purified on silica gel using 4% isopropanol in dichloromethane as eluent. The combined fractions containing the product may have residual amine contamination. If so, the fractions were concentrated via rotary evaporator and further purified by silica gel chromatography using a gradient of 1:1 ethyl acetate/hexanes to 5:5:1 ethyl acetate/hexanes/methanol solution as eluent to afford the product 8 as a foam (0.500 g, 30% yield).

Example K4

Diacid 6: A solution of dibenzylphosphonate 9 (8.0 g, 9.72 mmol) in ethanol (160 mL) and ethyl acetate (65 mL) under a nitrogen atmosphere and at room temperature was charged 10% Pd/C (1.60 g, 20 wt%). The mixture was stirred and evacuated by vacuum and purged with hydrogen several times. The contents were then placed under atmospheric pressure of hydrogen via a balloon. The reaction was monitored by TLC assay (SiO_2, 7:2.5:0.5 dichloromethane/methanol/ammonium hydroxide as eluent, product $R_f = 0.05$, visualization by UV) and was judged complete in 4 to 5 hours. The reaction mixture was filtered through a pad of celite to remove Pd/C and the filter cake rinsed with ethanol/ethyl acetate mixture (50 mL). The filtrate was concentrated via rotary evaporation followed by several co-evaporations using ethyl acetate (3 x 50 mL) to remove ethanol. The semi-solid diacid 6, free of ethanol, was carried forward to the next step without purification.

Example K5

Diphenylphosphonate 10: To a solution of diacid 6 (5.6 g, 8.71 mmol) in pyridine (58 mL) at room temperature was charged phenol (5.95 g, 63.1 mmol). To this mixture, while stirring, was charged dicyclohexylcarbodiimide (7.45 g, 36.0 mmol). The resulting cloudy, yellow mixture was placed in a 70-80°C oil bath. The reaction was monitored by TLC assay (SiO_2, 7:2.5:0.5 dichloromethane/methanol/ammonium hydroxide as eluent, diacid $R_f = 0.05$, visualization by UV for the disappearance of starting material. SiO_2, 60% ethyl acetate in hexanes as eluent, diphenyl $R_f = 0.40$, visualization by UV) and was judged complete in 2 hours. To the reaction mixture was charged isopropyl acetate (60 mL) to produce a white precipitation. The slurry was filtered through a pad of celite to remove the white precipitate and the filter cake rinsed with isopropyl acetate (25 mL). The filtrate was concentrated via rotary evaporator. To the resulting yellow oil was charged a premixed solution of water (58 mL) and 1N HCl (55 mL) followed by isopropyl acetate (145 mL). The mixture was stirred for one hour in an ice bath. After separating the layers, the aqueous layer was back extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated via rotary evaporator. The crude product oil was purified by silica gel column chromatography using 50% ethyl acetate in hexanes as eluent to afford the product 10 as a white foam (3.52 g, 51% yield). ^1H NMR ($CDCl_3$) δ 7.75 (d, 2H), 7.40-7.20 (m, 15H), 7.10 (d, 2H), 5.65 (d, 1H),

5.10-4.90 (m, 2H), 4.65 (d, 2H), 4.00-3.80 (m, 4H), 3.75-3.65 (m, 3H), 3.25-2.75 (m, 7H), 1.90-1.75 (m, 1H), 1.70-1.60 (m, 1H), 1.50-1.40 (m, 1H), 0.90 (d, 3H), 0.85 (d, 3H). ^{31}P NMR ($CDCl_3$) δ 10.9.

Example K6

Monophenyl 1: To a solution of diphenyl 10 (3.40 g, 4.28 mmol) in acetonitrile (170 mL) at 0°C was charged 1N sodium hydroxide (4.28 mL). The reaction was monitored by TLC assay (SiO_2, 7:2.5:0.5 dichloromethane/methanol/ammonium hydroxide as eluent, diphenyl R_f = 0.65, visualization by UV for the disappearance of starting material. Product monophenyl R_f = 0.80, visualization by UV). Additional 1N NaOH was added (if necessary) until the reaction was judged complete. To the reaction contents at 0°C was charged Dowex H^+ (Dowex 50WX8-200) (4.42 g) and stirred for 30 minutes at which time the pH of the mixture reached pH 1 (monitored by pH paper). The mixture was filtered to remove the Dowex resin and the filtrate was concentrated via rotary evaporation (water bath < 40°C). The resulting solution was co-evaporated with toluene to remove water (3 x 50 mL). The white foam was dissolved in ethyl acetate (8 mL) followed by slow addition of hexanes (16 mL) over 30 minutes to induce precipitation. A premixed solution of 2:1 hexnaes/ethyl acetate solution (39 mL) was charged to the precipitated material and stirred. The product 1 was filtered and rinsed with premixed solution of 2:1 hexanes/ethyl acetate solution (75 mL) and dried under vacuum to afford a white powder (2.84 g, 92% yield). ^{1}H NMR (CD_3OD) δ 7.80 (d, 2H), 7.40-7.30 (m, 2H), 7.20-7.15 (m, 11H), 5.55 (d, 1H), 4.50 (d, 2H), 3.95-3.85 (m, 1H), 3.80-3.60 (m, 5H), 3.45 (bd, 1H), 3.25-3.15 (m, 2H), 3.00-2.80 (m, 3H), 2.60-2.45 (m, 1H), 2.10-1.95 (m, 2H), 1.85-1.60 (m, 2H), 1.50-1.40 (m, 1H), 1.40-1.30 (m, 1H), 0.95 (d, 3H), 0.85 (d, 3H). ^{31}P NMR ($CDCl_3$) δ 13.8. The monophenyl product 1 is sensitive to silica gel. On contact with silica gel 1 converts to an unknown compound possessing ^{31}P NMR chemical shift of 8 ppm. However, the desired monophenyl product 1 can be regenerated by treatment of the unknown compound with 2.5 M NaOH in acetonitrile at 0°C for one hour followed by Dowex H^+ treatment as described above.

Example K7

Dibenzylphosphonate 9: To a solution of phenol 11 (6.45 g, 11.8 mmol) in tetrahydrofuran (161 mL) at room temperature was charged triflate reagent 12 (6.48 g, 15.3 mmol). Cesium carbonate (11.5 g, 35.3 mmol) was added and the mixture was stirred and

monitored by TLC assay (SiO_2, 5% methanol in dichloromethane as eluent, dibenzyl product R_f = 0.26, visualization by UV or ninhydrin stain and heat). Additional Cs_2CO_3 was added until the reaction was judged complete. To the reaction contents was charged water (160 mL) and the mixture extracted with ethyl acetate (2 x 160 mL). The combined organic layer was dried over sodium sulfate, filtered, and concentrated via rotary evaporator to afford a viscous oil. The crude oil was purified by silica gel column chromatography using a gradient of 100% dichloromethane to 1% methanol in dichloromethane to afford product 9 as a white foam (8.68 g, 90% yield). ^{1}H NMR ($CDCl_3$) δ 7.75 (d, 2H), 7.40-7.20 (m, 16H), 6.95 (d, 2H), 5.65 (d, 1H), 5.20-4.90 (m, 6H), 4.25 (d, 2H), 4.00-3.80 (m, 4H), 3.75-3.65 (m, 3H), 3.20-2.75 (m, 7H), 1.90-1.75 (m, 1H), 1.30-1.20 (m, 1H), 0.90 (d, 3H), 0.85 (d, 3H). ^{31}P NMR ($CDCl_3$) δ 19.1.

<u>Example K7a</u>

Hydroxyphenylsulfonamide 14: To a solution of methoxyphenylsulfonamide 13 (35.9 g, 70.8 mmol) in dichloromethane (3.5 L) at 0°C was charged boron tribromide (1M in DCM, 40.1 mL, 425 mmol). The reaction content was allowed to warm to room temperature, stirred over two hours, and monitored by TLC assay (SiO_2, 10% methanol in dichloromethane as eluent, dibenzyl product R_f = 0.16, visualization by UV). To the contents at 0°C was slowly charged propylene oxide (82 g, 1.42 mmol). Methanol (200 mL) was added and the reaction mixture was concentrated via rotary evaporator to afford a viscous oil. The crude product mixture was purified by silica gel column chromatography using 10% methanol in dichloromethane to afford the product 14 as a foam (22 g, 80% yield). ^{1}H NMR (DMSO) δ 7.60 (d, 2H), 7.30-7.20 (m, 5H), 6.95 (d, 2H), 3.90-3.75 (m, 1H), 3.45-3.20 (m, 5H), 3.00-2.55 (m, 5H), 2.50-2.40 (m, 1H), 1.95-1.85 (m, 1H), 0.85 (d, 3H), 0.80 (d, 3H).

<u>Example K8</u>

Cisfuran carbamate 16: To a solution of amine 14 (20.4 g, 52.0 mmol) in acetonitrile (600 mL) at room temperature was charged dimethylaminopyridine (13.4 g, 109 mmol) followed by cisfuran *p*-nitrophenylcarbonate reagent 15 (14.6 g, 49.5 mmol). The resulting solution was stirred at room temperature for at least 48 hours and monitored by TLC assay (SiO_2, 10% methanol in dichloromethane as eluent, cisfuran product R_f = 0.34, visualization by UV). The reaction mixture was concentrated via rotary evaporator. The crude product mixture was purified by silica gel column chromatography using a gradient of 60% ethyl acetate in hexanes to

70% ethyl acetate in hexanes to afford the product 16 as a solid (18.2 g, 64% yield). ^{1}H NMR (DMSO) δ 10.4 (bs, 1H), 7.60 (d, 2H), 7.30-7.10 (m, 6H), 6.95 (d, 2H), 5.50 (d, 1H), 4.85 (m, 1H), 3.85 (m, 1H), 3.70 (m, 1H), 3.65-3.50 (m, 4H), 3.30 (d, 1H), 3.05-2.95 (m, 2H), 2.80-2.65 (m, 3H), 2.50-2.40 (m, 1H), 2.00-1.90 (m, 1H), 1.45-1.20 (m, 2H), 0.85 (d, 3H), 0.80 (d, 3H).

Example Section L

Example L1

Monobenzyl phosphonate 2 A solution of dibenzylphosphonate 1(150 mg, 0.175mmol) was dissolved in toluene (1 mL), treated with DABCO (20 mg, 0.178 mmol) and was refluxed under N2 atmosphere (balloon) for 3 h. The solvent was removed and the residual was dissolved in aqueous HCl (5%). The aqueous layer was extracted with ethyl acetate and the organic layer was dried over sodium sulfate. After evaporation to yield the monobenzyl phosphonate 2 (107 mg, 80%) as a white powder. ^{1}H NMR (CD_3OD) δ 7.75 (d, J = 5.4 Hz, 2H), 7.42-7.31 (m, 5H) 7.16 (d, J = 5.4 Hz, 2H), 7.01 (d, J = 5.4 Hz, 2H), 6.86 (d, J = 5.4 Hz, 2H), 5.55 (d, J = 3.3 Hz, 1H), 5.14 (d, J = 5.1 Hz, 2H), 4.91 (m, 1H), 4.24-3.66 (m overlapping s, 11H), 3.45 (m, 2H), 3.14-2.82 (m, 6H), 2.49 (m, 1H), 2.01 (m, 1H), 1.51-1.34 (m, 2H), 0.92 (d, J = 3.9 Hz, 3H), 0.87 (d, J = 3.9 Hz, 3H); ^{31}P NMR (CD_3OD) δ 20.5; MS (ESI) 761 (M-H).

Example L2

Monobenzyl, ethyl phosphonate 3 To a solution of monobenzyl phosphonate 2 (100 mg, 0.13 mmol) in dry THF (5 mL) at room temperature under N_2 was added Ph_3P (136 mg, 0.52 mmol) and ethanol (30 μL, 0.52 mmol). After cooled to 0°C, DEAD (78μL, 0.52 mmol) was added. The mixture was stirred for 20 h at room temperature. The solvent was evaporated under reduced pressure and the residue was purified by using chromatograph on silica gel (10% to 30% ethyl acetate / hexane) to afford the monobenzyl, ethyl phosphonate 3 (66 mg, 64%) as white solid. ^{1}H NMR ($CDCl_3$) 7.70 (d, J = 8.7 Hz, 2H), 7.43-7.34 (m, 5H) 7.14 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.7Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 5.56 (d, J = 5.4 Hz, 1H), 5.19 (d, J = 8.7 Hz, 2H), 5.00 (m, 2H), 4.22-3.67 (m overlapping s, 13H), 3.18-2.76 (m, 7H), 1.82-1.54 (m, 3H), 1.33 (t, J = 7.0 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 19.8; MS (ESI) 813 (M+Na).

Example L3

Monoethyl phosphonate 4 A solution of monobenzyl, ethyl phosphonate 3 (60 mg) was dissolved in EtOAc (2 mL), treated with 10% Pd/C (6 mg) and was stirred under H_2 atmosphere (balloon) for 2h. The catalyst was removed by filtration through celite. The filtered was evaporated under reduced pressure, the residue was triturated with ether and the solid was

collected by filtration to afford the monoethyl phosphonate 4 (50 mg, 94%) as white solid. ^1H NMR (CD_3OD) 7.76 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.7Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 5.58 (d, J = 5.4 Hz, 1H), 5.90 (m, 1H), 4.22-3.67 (m overlapping s, 13H), 3.18-2.50 (m, 7H), 1.98(m, 1H), 1.56 (m, 2H), 1.33 (t, J = 6.9 Hz, 3H), 0.92 (d, J = 6.6Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CD_3OD) δ 18.7; MS (ESI) 700 (M-H).

Example L4

Monophenyl, ethyl phosphonate 5 To a solution of phosphonic acid 11 (800 mg, 1.19 mmol) and phenol (1.12 g, 11.9 mmol) in pyridine (8 mL) was added ethanol (69 μL, 1.19 mmol) and 1, 3-dicyclohexylcarbodiimide (1g, 4.8 mmol). The solution was stirred at 70°C for 2h. The reaction mixture was cooled to room temperature, then diluted with ethyl acetate (10 mL) and filtered. The filtrate was evaporated under reduced pressure to remove pyridine. The residue was dissolved in ethyl acetate and the organic phase was separated and washed with brine, dried over MgSO4, filtered and concentrated. The residue was purified by chromatography on silica gel to give monophenyl, ethyl phosphonate 5 (600 mg, 65%) as white solid. ^1H NMR ($CDCl_3$) 7.72 (d, J = 9 Hz, 2H), 7.36-7.18 (m, 5H), 7.15 (d, J = 8.7 Hz, 2H), 6.98 (d, J = 9Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.64 (d, J = 5.4 Hz, 1H), 5.00 (m, 2H), 4.34 (m, 4H), 3.94-3.67 (m overlapping s, 9H), 3.18-2.77 (m, 7H), 1.82-1.54 (m, 3H), 1.36 (t, J = 7.2 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 16.1; MS (ESI) 799 (M+Na).

Example L5

Sulfonamide 6 To a suspension of epoxide 5 (3 g, 8.12 mmol) in 2-propanol (30 mL) was added isobutylamine (8 mL, 81.2 mmol) and the solution was stirred at 80°C for 1 h. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH_2Cl_2 (40 mL) and cooled to 0°C. TEA (2.3 mL, 16.3mmol) was added followed by the addition of 4-nitrobenzenesulfonyl chloride (1.8 g, 8.13 mmol) in CH_2Cl_2 (5 mL) and the solution was stirred for 30 min at 0°C, warmed to room temperature and evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was recrystallized from EtOAc/hexane to give the sulfonamide 6 (4.6 g, 91%) as an off-white solid. MS (ESI) 650 (M+Na).

Example L6

Phenol 7 A solution of sulfonamide 6 (4.5 g, 7.1 mmol) in CH_2Cl_2 (50 mL) at 0°C was treated with BBr_3 (1M in CH_2Cl_2, 50mL). The solution was stirred at 0°C to room temperature for 48h. CH_3OH (10 mL) was carefully added. The solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic phase washed with saturated NaCl, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (10% - MeOH/CH_2Cl_2) to give the phenol 7 (2.5 g, 80%) as an off-white solid. MS (ESI) 528 (M+H).

Example L7

Carbamate 8 A solution of sulfonamide 7 (2.5 g, 5.7 mmol) in CH_3CN (100 mL) and was treated with proton-sponge (3 g, 14 mmol) and followed by (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (1.7 g, 5.7 mmol) at 0°C. After stirring for 48h at room temperature, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 10% HCl. The organic phase was washed with saturated NaCl, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (10% MeOH/CH_2Cl_2) affording the carbamate 8 (2.1g, 62 %) as a white solid. MS (ESI) 616 (M+Na).

Example L8

Diethylphosphonate 9 To a solution of carbamate 8 (2.1 g, 3.5 mmol) in CH_3CN (50 mL) was added Cs_2CO_3 (3.2 g, 9.8 mmol) and diethyltriflate (1.6g, 5.3 mmol). The mixture was stirred at room temperature for 1h. After removed the solvent, the residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (1% to 5% MeOH /CH_2Cl_2) to afford the diethylphosphonate 9 as a white solid: ^1H NMR ($CDCl_3$) δ 8.35 (d, J = 9 Hz, 2H), 7.96 (d, J = 9 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 5.63 (d, J = 5.1 Hz, 1H), 5.18-5.01 (m, 2H), 4.27-4.17 (m, 6H), 3.94-3.67 (m, 7H), 3.20-2.73 (m, 7H), 1.92-1.51 (m, 3H), 1.35 (t, J = 7.2 Hz, 6H), 0.88-0.85 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 19.2; MS (ESI) 756 (M+Na).

Example L9

Amine 10 A solution of diethylphosphonate 9 (1 g) was dissolved in EtOH (100 mL), treated with 10% Pd/C (300 mg) and was stirred under H_2 atmosphere (balloon) for 3h. The reaction was purged with N_2, and the catalyst was removed by filtration through celite. After evaporation of the filtrate, the residue was triturated with ether and the solid was collected by filtration to afford the amine 10 (920 mg, 96%) as a white solid. ^{1}H NMR ($CDCl_3$) ^{1}H NMR ($CDCl_3$) δ 7.41 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 8.4 Hz, 2H), 5.67 (d, J = 5.1 Hz, 1H), 5.13-5.05 (m, 2H), 4.42 (s, 2H), 4.29-4.20 (m, 6H), 4.00-3.69 (m, 7H), 3.00-2.66 (m, 7H), 1.80-1.69 (m, 3H), 1.38 (m, 6H), 0.94 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.4 Hz, 6H); ^{31}P NMR ($CDCl_3$) δ 19.4; MS (ESI) 736 (M+Na).

Compound	R_1	R_2
16a	Gly-Et	Gly-Et
16b	Gly-Bu	Gly-Bu
16j	Phe-Bu	Phe-Bu
16k	NHEt	NHEt

Example L10

Synthesis of Bisamidates 16a. A solution of phosphonic acid 11 (100 mg, 0.15 mmol) L-alanine ethyl ester hydrochloride (84 mg, 0.6 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph_3P (118 mg, 0.45 mmol) and 2,2'-dipyridyl disulfide (99 mg, 0.45 mmol) in pyridine (1 mL) stirring for 20h at room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH_2Cl_2). The purified product was suspended in ether and was evaporated under reduced pressure to afford bisamidate 16a (90 mg, 72%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz , 2H), 5.68 (d, J = 5.1 Hz,, 1H), 5.05 (m, 1H), 4.25 (d, J = 9.9 Hz, 2H), 4.19 (q, 4H), 3.99-3.65 (m overlapping s, 13H,), 3.41 (m, 1H), 3.20-2.81 (m, 7H), 1.85-1.60 (m, 3H), 1.27 (t, J = 7.2 Hz, 6H), 0.93 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 21.8; MS (ESI) 843 (M+H).

Example L11

Synthesis of Bisamidates 16b. A solution of phosphonic acid 11 (100 mg, 0.15 mmol) L-alanine n-butyl ester hydrochloride (101 mg, 0.6 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph_3P (118 mg, 0.45 mmol) and 2,2'-dipyridyl disulfide (99 mg, 0.45 mmol) in pyridine (1 mL) stirring for 20h at room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH_2Cl_2). The purified product was suspended in ether and was evaporated under reduced pressure to afford bisamidate 16b (100 mg, 74%) as a white solid: ^1H NMR ($CDCl_3$) δ 7.72 (d, J = 9 Hz, 2H), 7.15 (d, J = 9 Hz, 2H), 7.01 (d, J = 9 Hz, 2H), 6.87 (d, J = 9 Hz, 2H), 5.67 (d, J = 5.4 Hz, 1H), 5.05 (m, 1H), 4.96 (m, 1H), 4.25 (d, J = 9.9 Hz, 2H), 4.11 (t, J = 6.9 Hz, 4H), 3.99-3.71 (m overlapping s, 13H,), 3.41 (m, 1H), 3.20-2.80 (m, 7H), 1.87-1.60 (m, 7H), 1.42 (m, 4H), 0.96-0.88 (m, 12H); ^{31}P NMR ($CDCl_3$) δ 21.8; MS (ESI) 890 (M+H).

Example L12

Synthesis of Bisamidates 16j. A solution of phosphonic acid 11 (100 mg, 0.15 mmol) L-phenylalanine n-butyl ester hydrochloride (155 mg, 0.6 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph_3P (118 mg, 0.45 mmol) and 2,2'-dipyridyl disulfide (99 mg, 0.45 mmol) in pyridine (1 mL) stirring for 36h at room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH_2Cl_2). The purified product was suspended in ether and was evaporated under reduced pressure to afford bisamidate 16j (106 mg, 66%) as a white solid. ^1H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.31-7.10 (m, 12H), 7.01 (d, J = 9 Hz, 2H), 6.72 (d, J = 8.7 Hz, 2H), 5.67 (d, J = 5.1 Hz, 1H), 5.05 (m, 1H), 4.96 (m, 1H), 4.35-3.98 (m., 7H), 3.90-3.61 (m overlapping s, 10H,), 3.19-2.78 (m, 11H), 1.87-1.25 (m, 11H), 0.96-0.88 (m, 12H); ^{31}P NMR ($CDCl_3$) δ 19.3; MS (ESI) 1080 (M+H).

Example L13

Synthesis of Bisamidates 16k. A solution of phosphonic acid 11 (80 mg, 0.12 mmol), ethylamine (0.3 mL,2M in THF, 0.6 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph_3P

(109 mg, 0.42 mmol) and 2,2'-dipyridyl disulfide (93 mg, 0.42 mmol) in pyridine (1 mL) stirring for 48h at room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH_2Cl_2). The purified product was suspended in ether and was evaporated under reduced pressure to afford bisamidate 16k (60 mg, 70%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz , 2H), 5.67 (d, J = 5.1 Hz, 1H), 5.05-4.95 (m, 2H), 4.15 (d, J = 9.6 Hz, 2H), 3.99-3.72 (m overlapping s, 9H,), 3.18-2.81 (m, 11H), 2.55 (br, 1H), 1.85-1.65 (m, 3H), 1.18 (t, J = 7.2 Hz, 6H), 0.93 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 21.6; MS (ESI) 749 (M+Na).

Compound	**R_1**	**R_2**
30a	OPh	Ala-Me
30b	OPh	Ala-Et
30c	OPh	(D)-Ala-iPr
30d	OPh	Ala-Bu
30e	OBn	Ala-Et

Example L14

Monoamidate 30a (R1 = OPh, R2 = Ala-Me) To a flask was charged with monophenyl phosphonate 29 (75 mg, 0.1 mmol), L-alanine methyl ester hydrochloride (4.0 g, 22 mmol) and 1, 3-dicyclohexylcarbodiimide (84 mg, 0.6 mmol), then pyridine (1 mL) was added under N2. The resulted mixture was stirred at 60 – 70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was partitioned between ethyl acetate and HCl (0.2 N), the ethyl acetate phase was washed with water and $NaHCO_3$, dried over Na_2SO_4 filtered and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate/hexane 1:5) to give 30a (25 mg, 30%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.24 (m, 5H) 7.19-7.15 (m, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.90-6.83 (m, 2H), 5.65 (d, J = 5.1 Hz, 1H), 5.01 (m, 2H), 4.30 (m, 2H), 3.97-3.51 (m overlapping s, 12H), 3.20-2.77 (m, 7H), 1.81 (m, 1H), 1.58 (m, 3H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.4 and 19.3; MS (ESI) 856 (M+Na).

Example L15

Monoamidate 30b (R1 = OPh, R2 = Ala-Et) was synthesized in the same manner in 35% yield. ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.24 (m, 5H) 7.19-7.15 (m, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.90-6.83 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.01 (m, 3H), 4.30 -3.67 (m overlapping s, 14H), 3.18-2.77 (m, 7H), 1.81-1.35 (m, 6H), 1.22 (m, 3H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.4 and 19.3; MS (ESI) 870 (M+Na).

Example L16

Monoamidate 30c (R1 = OPh, R2 = (D)-Ala-iPr) was synthesized in the same manner in 52% yield. Isomer A ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.24 (m, 5H) 7.19-7.15 (m, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.90-6.83 (m, 2H), 5.66 (m,, 1H), 5.01 (m, 3H), 4.30 -3.67 (m overlapping s, 14H), 3.18-2.77 (m, 7H), 1.81-1.35 (m, 6H), 1.23 (m, 6H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.4; MS (ESI) 884 (M+Na). Isomer B ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.24 (m, 5H) 7.19-7.15 (m, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.90-6.83 (m, 2H), 5.66 (m,, 1H), 5.01 (m, 3H), 4.30 -3.67 (m overlapping s, 14H), 3.18-2.77 (m, 7H), 1.81-1.35 (m, 6H), 1.23 (m, 6H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 19.3; MS (ESI) 884 (M+Na).

Example L17

Monoamidate 30d (R1 = OPh, R2 = Ala-Bu) was synthesized in the same manner in 25% yield. ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.24 (m, 5H) 7.19-7.15 (m, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.90-6.83 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.01 (m, 3H), 4.30 -3.67 (m overlapping s, 16H), 3.18-2.77 (m, 7H), 1.81-1.35 (m, 8H), 1.22 (m, 3H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.4 and 19.4; MS (ESI) 898 (M+Na).

Example L18

Monoamidate 30e (R1 = OBn, R2 = Ala-Et) To a flask was charged with monobenzyl phosphonate 2 (76 mg, 0.1 mmol), L-alanine methyl ester hydrochloride (4.0 g, 22 mmol) and 1, 3-dicyclohexylcarbodiimide (84 mg, 0.6 mmol), then pyridine (1 mL) was added under N2. The resulted mixture was stirred at 60 – 70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was partitioned between ethyl acetate and HCl (0.2 N), the ethyl acetate phase was washed with

water and $NaHCO_3$, dried over Na_2SO_4 filtered and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate / hexane 1:5) to give 30a (25 mg, 30%) as a white solid. ^1H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.38-7.34 (m, 5H), 7.13 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.86-6.80 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.15-5.01 (m, 5H), 4.30 - 3.67 (m overlapping s, 14H), 3.18-2.77 (m, 7H), 1.81-1.35 (m, 6H), 1.22 (m, 3H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 23.3 and 22.4; MS (ESI) 884 (M+Na).

Compound	R_1	R_2
31a	OPh	Lac-iPr
31b	OPh	Lac-Et
31c	OPh	Lac-Bu
31d	OPh	(R)-Lac-Me
31e	OPh	(R)-Lac-Et

Example L19

Monolactate 31a (R1 = OPh, R2 = Lac-iPr): To a flask was charged with monophenyl phosphonate 29 (1.5 g, 2 mmol), isopropyl-(s)-lactate (0.88 mL, 6.6 mmol) and 1, 3-dicyclohexylcarbodiimide (1.36 g, 6.6 mmol), then pyridine (15 mL) was added under N_2. The resulted mixture was stirred at 60 – 70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was washed with ethyl acetate and the combined organic phase was washed with NH_4Cl, brine and water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate / CH_2Cl_2 1:5) to give 31a (1.39g, 81%) as a white solid. Isomer A ^1H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.19 (m, 5H), 7.15 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 5.65 (d, J= 5.4 Hz, 1H), 5.15-5.00 (m, 4H), 4.56-4.44 (m, 2H), 3.96 -3.68 (m overlapping s, 9H), 3.13-2.78 (m, 7H), 1.81-1.23 (m, 6H), 1.22 (m, 6H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 17.4; MS (ESI) 885 (M+Na). Isomer B ^1H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.19 (m, 5H), 7.14 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.64 (d, J= 5.4 Hz, 1H), 5.15-5.00 (m, 4H), 4.53 -4.41 (m, 2H), 3.96 -3.68 (m overlapping s, 9H), 3.13-2.78 (m, 7H), 1.81-1.23 (m, 6H), 1.22 (m, 6H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 15.3; MS (ESI) 885 (M+Na).

Example L20

Monolactate 31b (R1 = OPh, R2 = Lac-Et) was synthesized in the same manner in 75% yield. ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.14 (m, 7H), 6.99 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.63 (m, 1H), 5.19-4.95 (m, 3H), 4.44-4.40 (m, 2H), 4.17-4.12 (m, 2H), 3.95 -3.67 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.58 (m, 6H), 1.23 (m, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 17.5 and 15.4; MS (ESI) 872 (M+Na).

Example L21

Monolactate 31c (R1 = OPh, R2 = Lac-Bu) was synthesized in the same manner in 58% yield. Isomer A ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.19 (m, 5H), 7.14 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 5.63 (d, J= 5.4 Hz, 1H), 5.15-5.00 (m, 3H), 4.56-4.51 (m, 2H), 4.17-4.10 (m, 2H), 3.95 -3.67 (m overlapping s, 9H), 3.10-2.77 (m, 7H), 1.81-1.23 (m, 10H), 1.23 (m, 6H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 17.3; MS (ESI) 899 (M+Na). Isomer B ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.19 (m, 5H), 7.14 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 5.64 (d, J= 5.4 Hz, 1H), 5.15-5.00 (m, 3H), 4.44 -4.39 (m, 2H), 4.17-4.10 (m, 2H), 3.95 -3.67 (m overlapping s, 9H), 3.10-2.77 (m, 7H), 1.81-1.23 (m, 10H), 1.23 (m, 6H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 15.3; MS (ESI) 899 (M+Na).

Example L22

Monolactate 31d (R1 = OPh, R2 = (R)-Lac-Me): To a stirred solution of monophenyl phosphonate 29 (100 mg, 0.13 mmol) in 10 mL of THF at room temperature under N_2 was added methyl-(S)-lactate (54 mg, 0.52 mmol) and Ph_3P (136 mg g,, 0.52 mmol), followed by DEAD (82μL, 0.52 mmol). After 2 h, the solvent was removed under reduced pressure, and the resulting crude mixture was purified by chromatography on silica gel (ethyl acetate / hexane 1:1) to give 31d (33 mg, 30%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.14 (m, 7H), 6.99 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.63 (m, 1H), 5.19-4.95 (m, 3H), 4.44-4.40 (m, 2H), 3.95 -3.64 (m overlapping s, 12H), 3.15-2.77 (m, 7H), 1.81-1.55 (m, 4H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 17.4 and 15.3; MS (ESI) 857 (M+Na).

Example L23

Monolactate 31e (R1 = OPh, R2 = (R)-Lac-Et): To a stirred solution of monophenyl phosphonate 29 (50 mg, 0.065 mmol) in 2.5 mL of THF at room temperature under N_2 was added ethyl-(s)-lactate (31 mg, 0.52 mmol) and Ph_3P (68 mg g, 0.26 mmol), followed by DEAD (41 μL, 0.52 mmol). After 2 h, the solvent was removed under reduced pressure, and the resulting crude mixture was purified by chromatography on silica gel (ethyl acetate / hexane 1:1) to give 31e (28 mg, 50%) as a white solid. ^1H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.14 (m, 7H), 6.99 (d, J = 8.7 Hz, 2H), 6.85(m, 2H), 5.63 (m, 1H), 5.19-4.95 (m, 3H), 4.44-4.40 (m, 2H), 4.17-4.12 (m, 2H), 3.95 -3.67 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.58 (m, 6H), 1.23 (m, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 17.5 and 15.4; MS (ESI) 872 (M+Na).

Example L24

Monolactate 32 (R1 = OBn, R2 = (S)-Lac-Bn): To a stirred solution of monobenzyl phosphonate 2 (76 mg, 0.1 mmol) in 0.5 mL of DMF at room temperature under N_2 was added benzyl-(s)-lactate (27 mg, 0.15 mmol) and PyBOP (78 mg, 0.15mmol), followed by DIEA (70μL, 0.4 mmol). After 3 h, the solvent was removed under reduced pressure, and the resulting crude mixture was purified by chromatography on silica gel (ethyl acetate / hexane 1:1) to give 32 (46 mg, 50%) as a white solid. ^1H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.38-7.44 (m, 10H), 7.13 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 6.81(m, 2H), 5.63 (d, J = 5.1 Hz, 1H), 5.23-4.92 (m, 7H), 4.44-22 (m, 2H), 3.96 -3.67 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.58 (m, 6H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.8 and 19.6; MS (ESI) 947 (M+Na).

Example L25

Monolactate 33 (R1 = OBn, R2 = (R)-Lac-Bn): To a stirred solution of monobenzyl phosphonate 2 (76 mg, 0.1 mmol) in 5 mL of THF at room temperature under N_2 was added benzyl-(s)-lactate (72 mg, 0.4 mmol) and Ph_3P (105 mg g, 0.4mmol), followed by DEAD (60μL, 0.4 mmol). After 20 h, the solvent was removed under reduced pressure, and the resulting crude mixture was purified by chromatography on silica gel (ethyl acetate / hexane 1:1) to give 33 (44 mg, 45%) as a white solid. ^1H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.38-7.44 (m, 10H),

7.13 (m, 2H), 6.99 (d, J = 8.7 Hz, 2H), 6.81(m, 2H), 5.63 (m, 1H), 5.23-4.92 (m, 7H), 4.44-22 (m, 2H), 3.96 -3.67 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.58 (m, 6H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.8 and 19.6; MS (ESI) 947 (M+Na).

Example L26

Monophosphonic acid 34: A solution of monobenzyllactate 32 (20 mg) was dissolved in EtOH/ EtOAc (3 mL/1 mL), treated with 10% Pd/C (4 mg) and was stirred under H2 atmosphere (balloon) for 1.5 h. The catalyst was removed by filtration through celite. The filtered was evaporated under reduced pressure, the residue was triturated with ether and the solid was collected by filtration to afford the monophosphonic acid 33 (15 mg, 94%) as a white solid. ^{1}H NMR (CD_3OD) δ 7.76 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 5.69 (d, J = 5.7 Hz, 1H), 5.03-4.95 (m, 2H), 4.20 (m, 2H), 3.90 -3.65 (m overlapping s, 9H), 3.41 (m, 2H), 3.18-2.78 (m, 5H), 2.44 (m, 1H), 2.00 (m, 1H), 1.61-1.38 (m, 5H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD_3OD) δ 18.0; MS (ESI) 767 (M+Na).

Example L27

Monophosphonic acid 35: A solution of monobenzyllactate 33(20 mg) was dissolved in EtOH (3 mL), treated with 10% Pd/C (4 mg) and was stirred under H2 atmosphere (balloon) for 1h. The catalyst was removed by filtration through celite. The filtered was evaporated under reduced pressure, the residue was triturated with ether and the solid was collected by filtration to afford the monophosphonic acid 35 (15 mg, 94%) as a white solid. ^{1}H NMR (CD_3OD) δ 7.76 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 5.69 (d, J = 5.7 Hz, 1H), 5.03-4.95 (m, 2H), 4.20 (m, 2H), 3.90 -3.65 (m overlapping s, 9H), 3.41 (m, 2H), 3.18-2.78 (m, 5H), 2.44 (m, 1H), 2.00 (m, 1H), 1.61-1.38 (m, 5H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD_3OD) δ 18.0; MS (ESI) 767 (M+Na).

Example L28

Synthesis of Bislactate 36: A solution of phosphonic acid 11 (100 mg, 0.15 mmol) isopropyl-(S)-lactate (79 mg, 0.66 mmol) was dissolved in pyridine (1 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph_3P (137 mg, 0.53 mmol) and 2,2'-dipyridyl disulfide (116 mg, 0.53 mmol) in pyridine (1 mL)

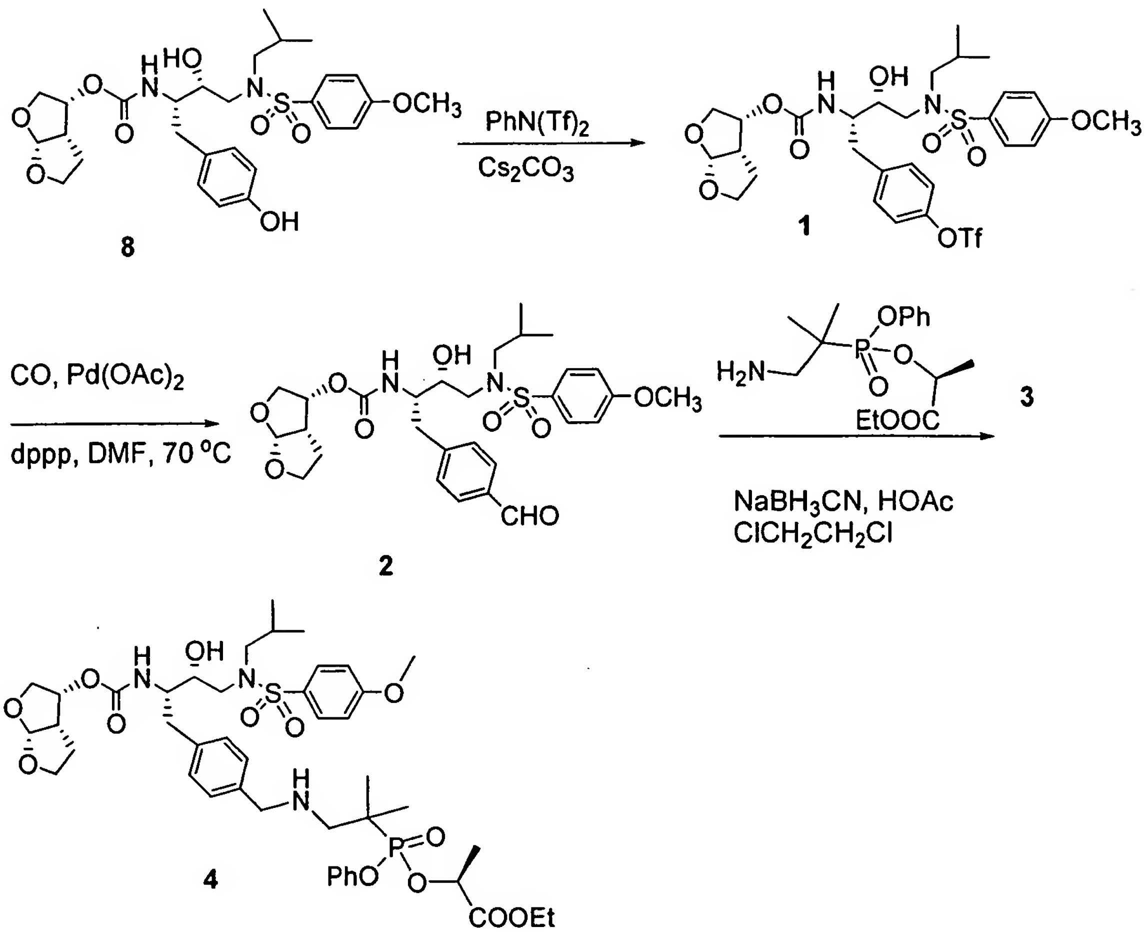
stirring for 20h at room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH_2Cl_2). The purified product was suspended in ether and was evaporated under reduced pressure to afford bislactate 36 (42 mg, 32%) as a white solid: ^1H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.14 (d, J = 8.7 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 5.66 (d, J = 5.1 Hz, 1H), 5.05 (m, 3H), 4.25 (d, J = 9.9 Hz, 2H), 4.19 (q, 4H), 3.99-3.65 (m overlapping s, 9H,), 3.41 (m, 1H), 3.20-2.81 (m, 7H), 1.85-1.60 (m, 3H),1.58 (m, 6H), 1.26 (m, 12H), 0.93 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 21.1; MS (ESI) 923 (M+Na).

<u>Example L29</u>

Triflate derivative **1**: A THF-CH_2Cl_2 solution (30mL-10 mL) of **8** (4 g, 6.9 mmol), cesium carbonate (2.7 g, 8 mmol), and N-phenyltrifluoromethane sulfonimide (2.8 g, 8 mmol) was reacted overnight. The reaction mixture was worked up, and concentrated to dryness to give crude triflate derivative **1**.

Aldehyde **2**: Crude triflate **1** (4.5 g, 6.9 mmole) was dissolved in DMF (20 mL), and the solution was degassed (high vacuum for 2 min, Ar purge, repeat 3 times). Pd(OAc)2 (0.12 g, 0.27 mmol), and bis(diphenylphosphino)propane (dppp, 0.22 g, 0.27 mmol) were added and the solution was heated to 70°C. Carbon monoxide was rapidly bubbled through the solution, then under 1 atmosphere of carbon monoxide. To this solution were slowly added TEA (5.4 mL, 38 mmol), and triethylsilane (3 mL, 18 mmol). The resulting solution was stirred overnight at room temperature. The reaction mixture was worked up, and purified on silica gel column chromatograph to afford aldehyde **2** (2.1 g, 51%). (Hostetler, *et al. J. Org. Chem.*, 1999. 64, 178-185).

Lactate prodrug **4**: Compound 4 is prepared as described above procedure for 3a-e by the reductive amination between 2 and 3 with $NaBH_3CN$ in 1,2-dichloroethane in the presence of HOAc.



Example L30

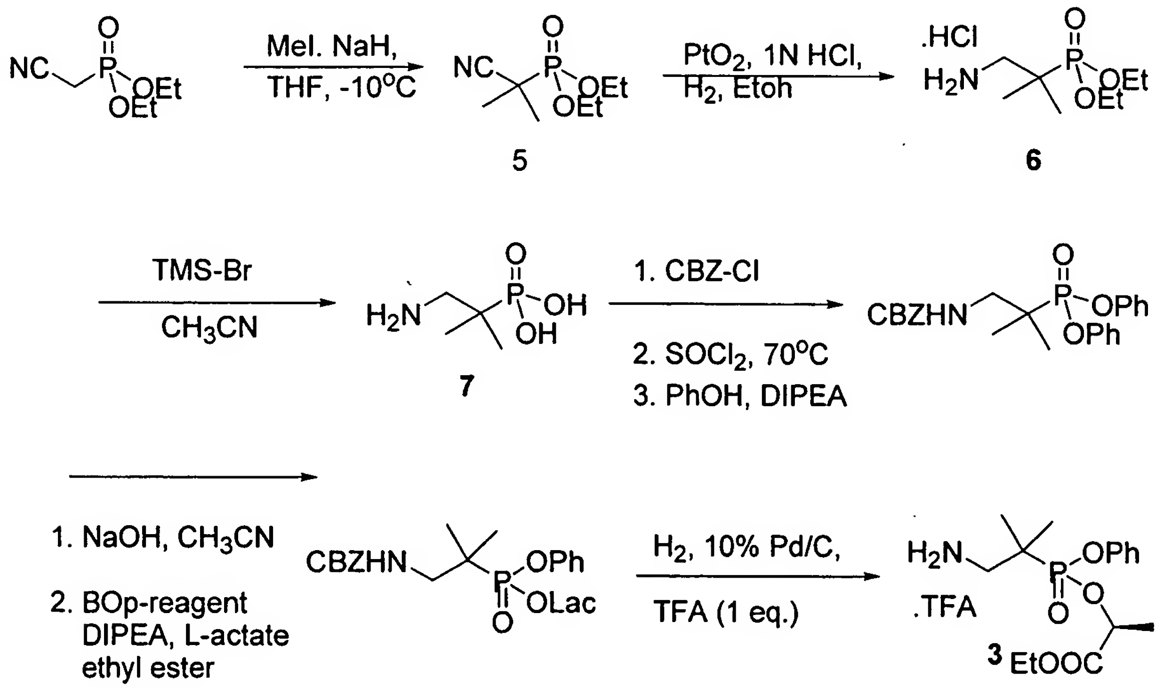
Preparation of compound **3** Diethyl (cyano(dimethyl)methyl) phosphonate **5**: A THF solution (30 mL) of NaH (3.4 g of 60% oil dispersion, 85 mmole) was cooled to –10°C, followed by the addition of diethyl (cyanomethyl)phosphonate (5g, 28.2 mmol) and iodomethane (17 g, 112 mmol). The resulting solution was stirred at –10°C for 2 hr, then 0°C for 1 hr, was worked up, and purified to give dimethyl derivative **5** (5 g, 86%).

Dietyl (2-amino-1,1-diemthyl-ethyl)phosphonate **6**: Compound **5** was reduced to amine derivative **6** by the described procedure (*J. Med. Chem.* 1999, 42, 5010-5019).

A ethanol (150 mL) and 1N HCl aqueous solution (22 mL) of 5 (2.2 g, 10.7 mmol) was hydrogenated at 1 atmosphere in the presence of PtO_2 (1.25 g) at room temperature overnight. The catalyst was filtered through a celite pad. The filtrate was concentrated to dryness, to give crude **6** (2.5g, as HCl salt).

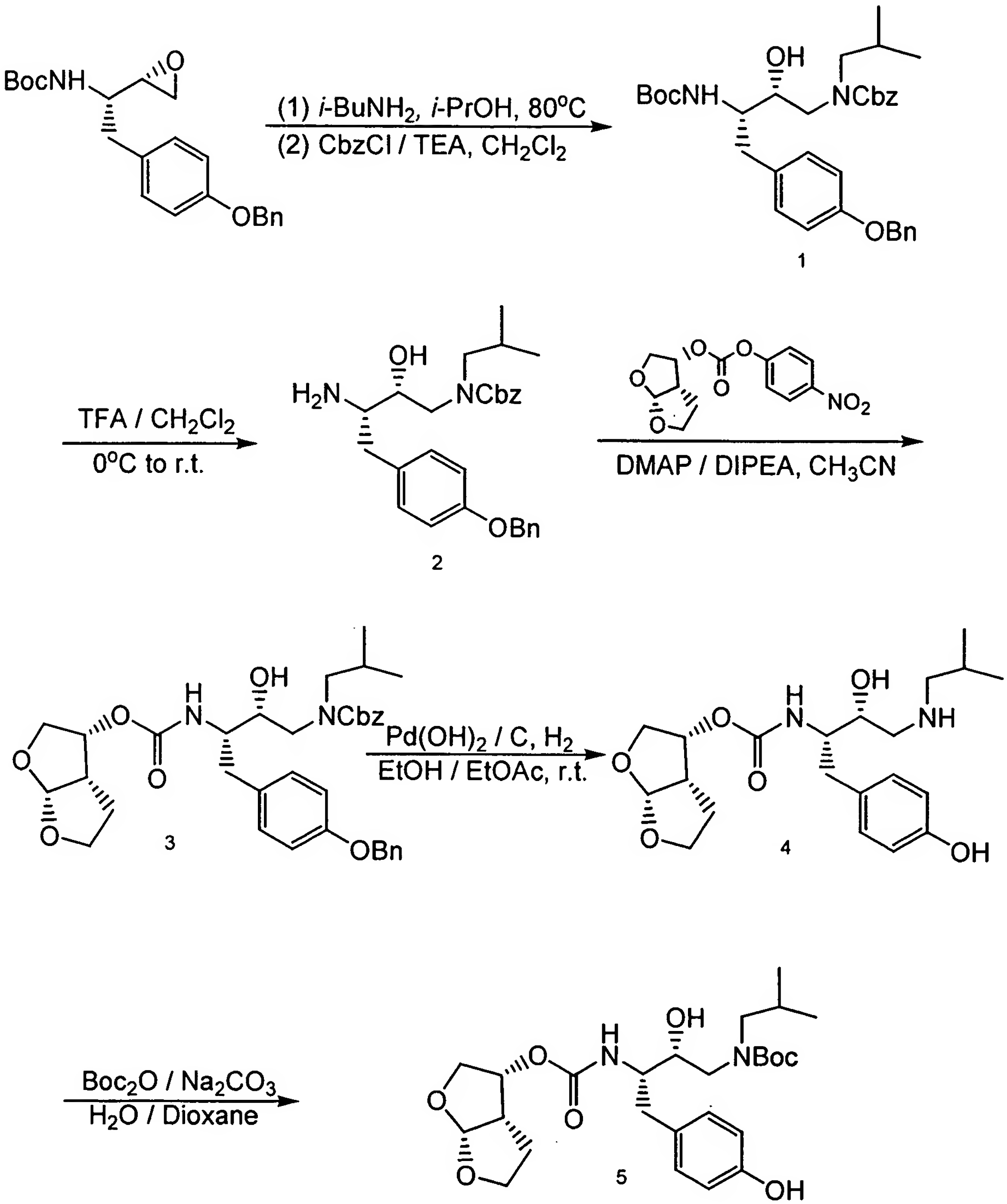
2-Amino-1,1-dimethyl-ethyl phosphonic acid **7**: A CH_3CN (30 mL) of crude **6** (2.5 g) was cooled to 0°C, and treated with TMSBr (8 g, 52 mmol) for 5 hr. The reaction mixture was stirred with methanol for 1.5 hr at room temperature, concentrated, recharged with methanol, concentrated to dryness to give crude **7** which was used for next reaction without further purification.

Lactate phenyl (2-amino-1,1-diemthyl-ethyl)phosphonate **3**: Compound **3** is synthesized according to the procedures described in a previous scheme for the preparation of a lactate phenyl 2-aminoethyl phosponate. Compound **7** is protected with CBZ, followed by the reaction with thionyl chloride at 70°C. The CBZ protected dichlorodate is reacted phenol in the presence of DIPEA. Removal of one phenol, follow by coupling with ethyl L-lactate leads N-CBZ-2-amino-1,1-dimethyl-ethyl phosphonated derivative. Hydrogenation of N-CBZ derivative at 1 atmosphere in the presence of 10% Pd/C and 1 equivalent of TFA affords compound **3** as TFA salt.

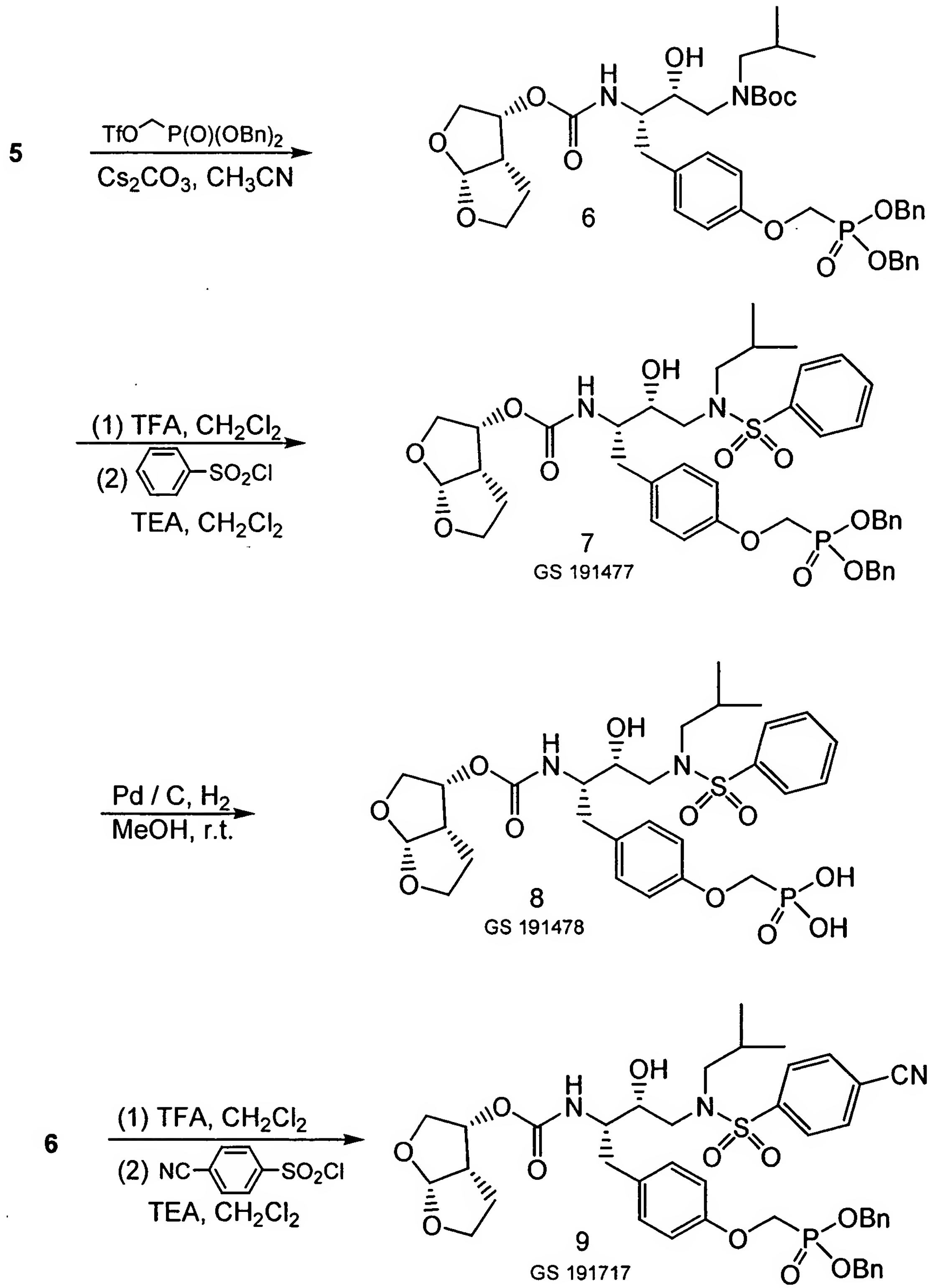


Example Section M

Scheme M1

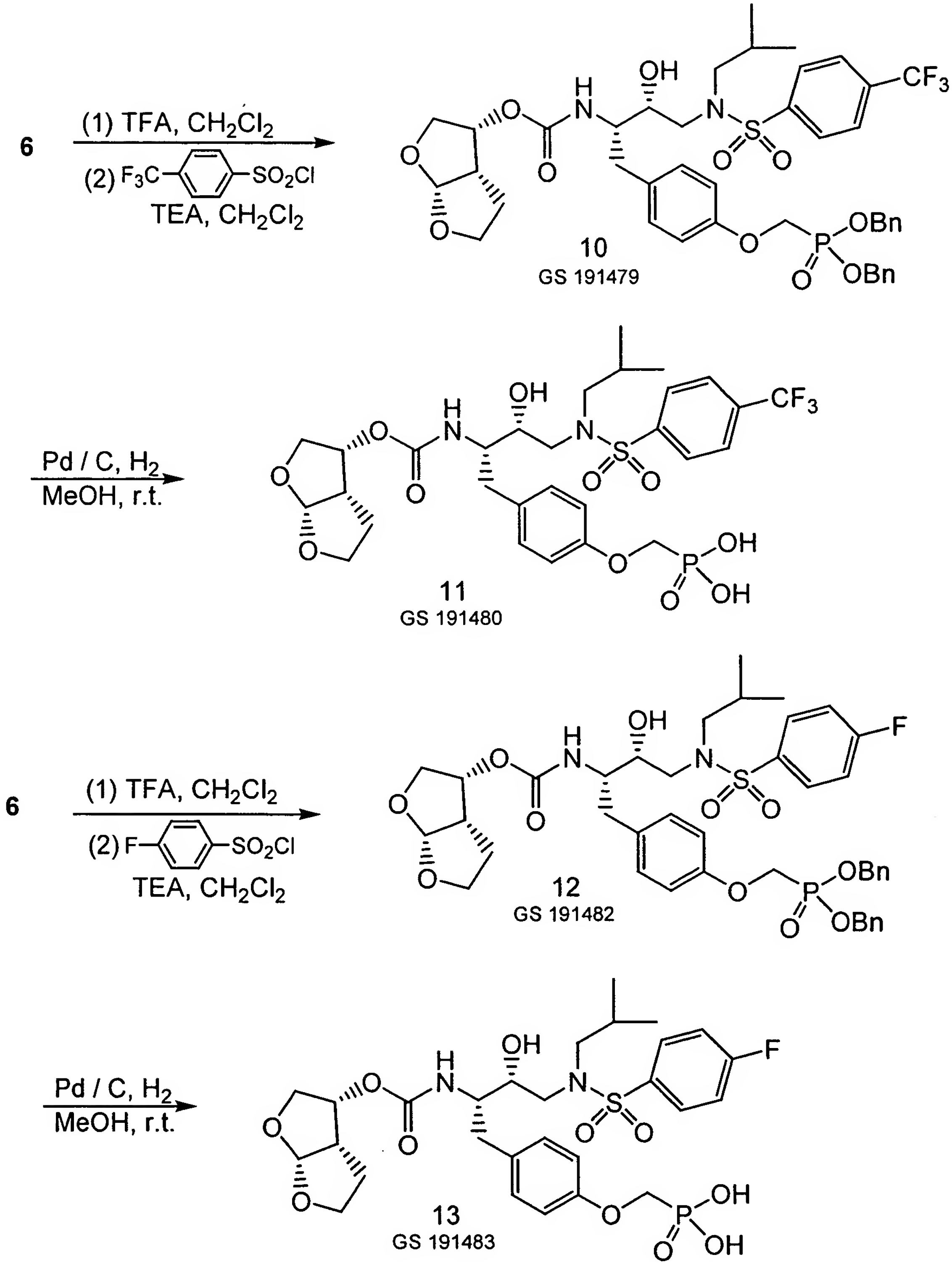


Scheme M2

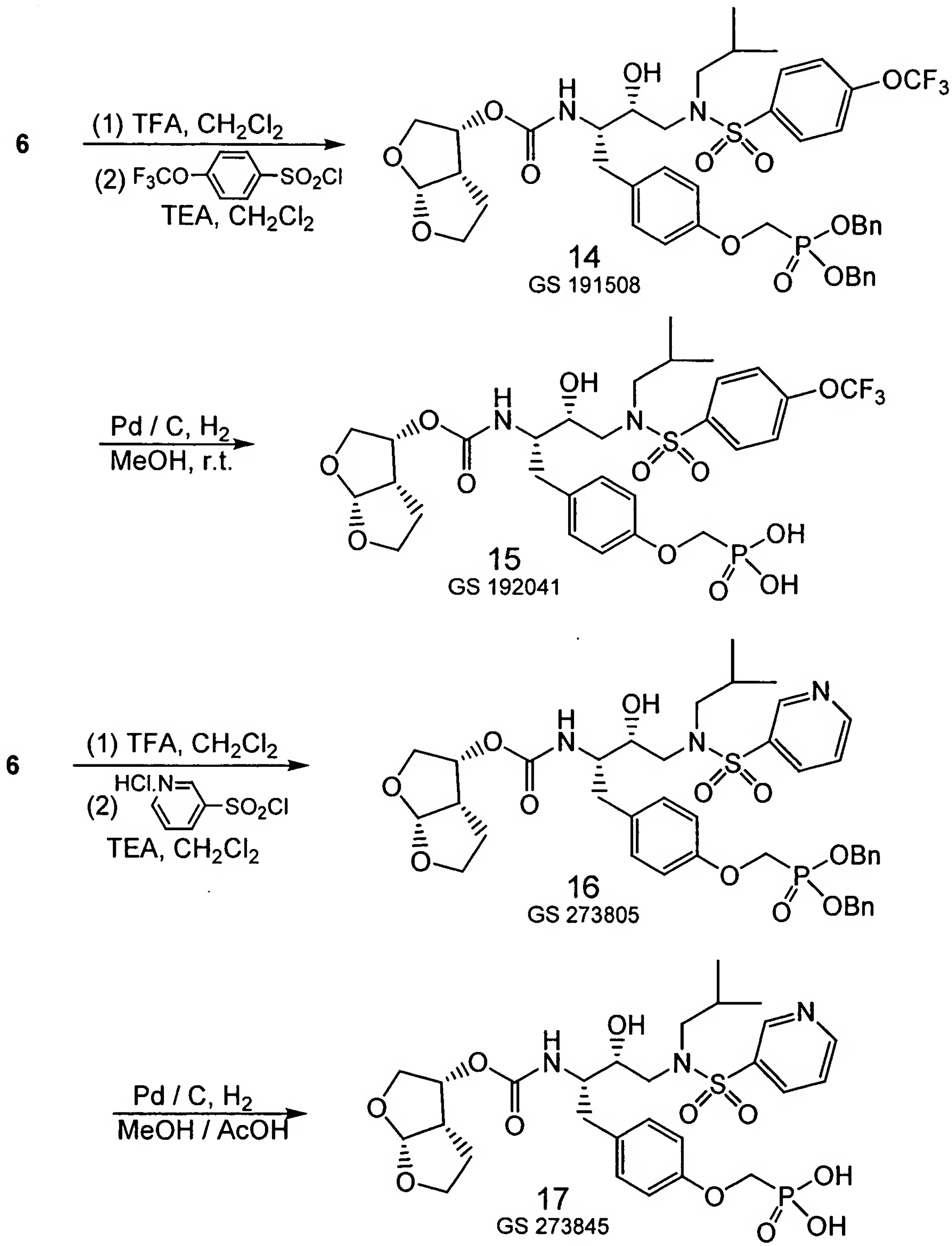


5
TfO P(O)(OBn)2
Cs2CO3, CH3CN
6
(1) TFA, CH2Cl2
(2) SO2Cl
TEA, CH2Cl2
7
GS 191477
Pd / C, H2
MeOH, r.t.
8
GS 191478
6
(1) TFA, CH2Cl2
(2) NC SO2Cl
TEA, CH2Cl2
9
GS 191717

Scheme M3

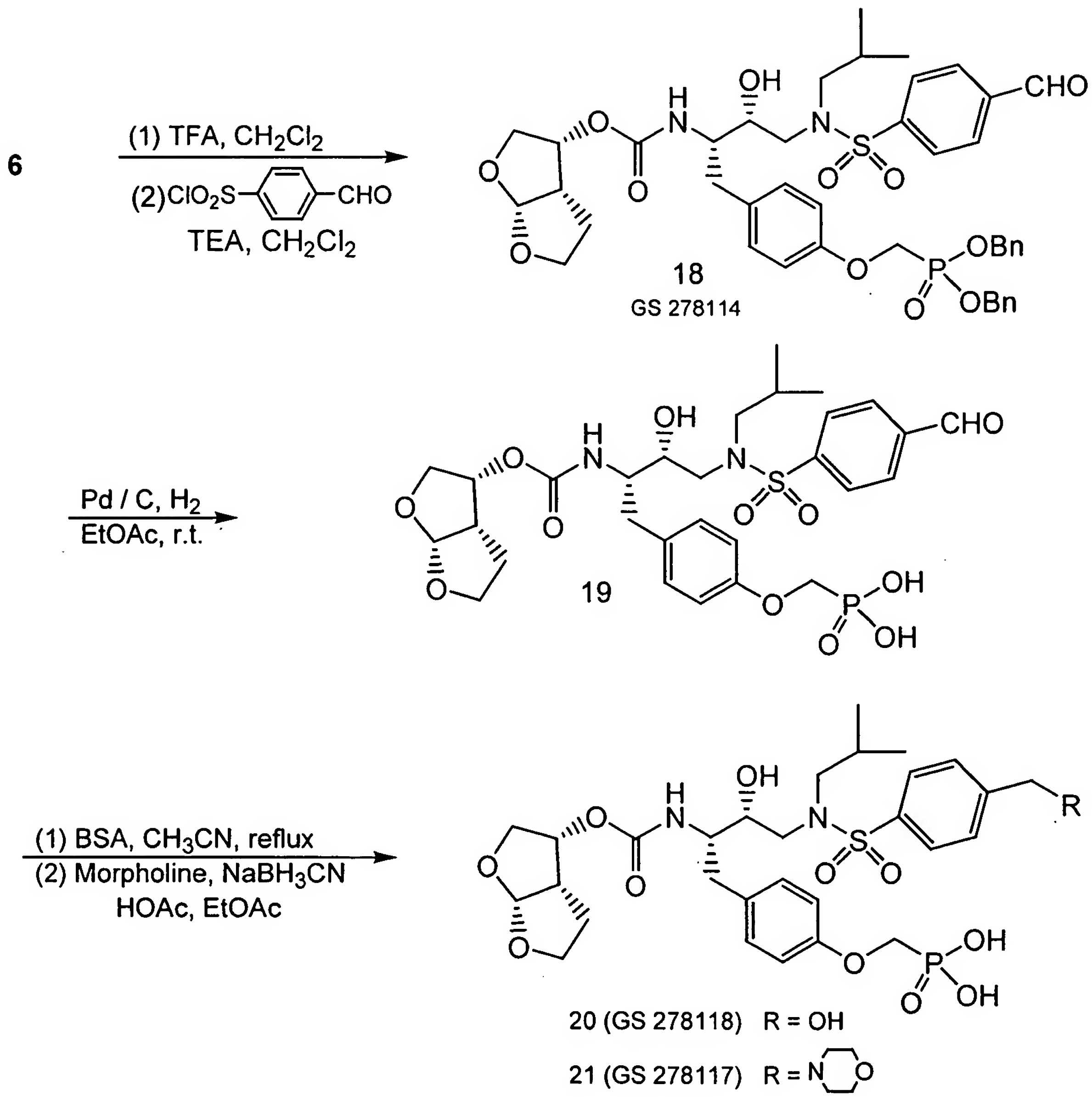

6
(1) TFA, CH2Cl2
(2) F3C–C6H4–SO2Cl
TEA, CH2Cl2
10
GS 191479
Pd / C, H2
MeOH, r.t.
11
GS 191480
6
(1) TFA, CH2Cl2
(2) F–C6H4–SO2Cl
TEA, CH2Cl2
12
GS 191482
Pd / C, H2
MeOH, r.t.
13
GS 191483

Scheme M4



6
(1) TFA, CH_2Cl_2
(2) F_3CO-C6H4-SO_2Cl
TEA, CH_2Cl_2
OH
H
N
O
O
O
O
N
S
O
O
OCF3
O
P
OBn
OBn
O
14
GS 191508
Pd / C, H_2
MeOH, r.t.
OH
OCF3
P
OH
OH
15
GS 192041
6
(1) TFA, CH_2Cl_2
(2) HCl.N
SO_2Cl
TEA, CH_2Cl_2
N
OBn
OBn
16
GS 273805
Pd / C, H_2
MeOH / AcOH
OH
OH
17
GS 273845

Scheme M5



Example M1

Cbz Amide 1: To a suspension of epoxide (34 g, 92.03 mmol) in 2-propanol (300 mL) was added isobutylamine (91.5 mL, 920 mmol) and the solution was refluxed for 1 h. The solution was evaporated under reduced pressure and the crude solid was dried under vacuum to give the amine (38.7 g, 95%) which was dissolved in CH_2Cl_2 (300 mL) and cooled to 0°C. Triethylamine (18.3 mL, 131 mmol) was added followed by the addition of benzyl chloroformate (13.7 mL, 96.14 mmol) and the solution was stirred for 30 min at 0°C, warmed to room temperature overnight, and evaporated under reduced pressure. The residue was partitioned

between EtOAc and 0.5 M H_3PO_4. The organic phase was washed with saturated $NaHCO_3$, brine, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (1/2-EtOAc/hexane) to give the Cbz amide (45.37 g, 90%) as a white solid.

Example M2

Amine 2: A solution of Cbz amide 1 (45.37 g, 78.67 mmol) in CH_2Cl_2 (160 mL) at 0°C was treated with trifluoroacetic acid (80 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. Volatiles were evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5 N NaOH (2 x), water (2 x), saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure to give the amine (35.62 g, 95%) as a white solid.

Example M3

Carbamate 3: To a solution of amine 2 (20.99 g, 44.03 mmol) in CH_3CN (250 mL) at 0°C was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (13.00 g, 44.03 mmol, prepared according to Ghosh *et al. J. Med. Chem.* 1996, *39*, 3278.), *N,N*-diisopropylethylamine (15.50 mL, 88.06 mmol) and 4-dimethylaminopyridine (1.08 g, 8.81 mmol). The reaction mixture was stirred at 0°C for 30 min and then warmed to room temperature overnight. The reaction solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5 N NaOH (2 x), 5% citric acid (2 x), saturated $NaHCO_3$, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the carbamate (23.00 g, 83%) as a white solid.

Example M4

Amine 4: To a solution of 3 (23.00 g, 36.35 mmol) in EtOH (200 mL) and EtOAc (50 mL) was added 20% $Pd(OH)_2/C$ (2.30 g). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 3 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the amine (14.00 g, 94%) as a white solid.

Example M5

Phenol 5: To a solution of amine 4 (14.00 g, 34.27 mmol) in H_2O (80 mL) and 1,4-dioxane (80 mL) at 0°C was added Na_2CO_3 (5.09 g, 47.98 mmol) and di-*tert*-butyl dicarbonate (8.98 g, 41.13 mmol). The reaction mixture was stirred at 0°C for 2 h and then warmed to room temperature for 30 min. The residue was partitioned between EtOAc and H_2O. The organic layer was dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% $MeOH/CH_2Cl_2$) to give the phenol (15.69 g, 90%) as a white solid.

Example M6

Dibenzylphosphonate 6: To a solution of phenol 5 (15.68 g, 30.83 mmol) in CH_3CN (200 mL) was added Cs_2CO_3 (15.07 g, 46.24 mmol) and triflate (17.00 g, 40.08 mmol). The reaction mixture was stirred at room temperature for 1 h, the salt was filtered off, and the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the dibenzylphosphonate (15.37 g, 73%) as a white solid.

Example M7

Sulfonamide 7: A solution of dibenzylphosphonate 6 (0.21 g, 0.26 mmol) in CH_2Cl_2 (0.5 mL) at 0°C was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C. Triethylamine (0.15 mL, 1.04 mmol) was added followed by the treatment of benzenesulfonyl chloride (47 mg, 0.26 mmol). The solution was stirred for 1 h at 0°C and the product was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the sulfonamide 7 (0.12 g, 55%, GS 191477) as a white solid: ^{1}HNMR ($CDCl_3$) δ 7.79 (dd, 2H), 7.61-7.56 (m, 3H), 7.38-7.36 (m, 10H), 7.13 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.4 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.18 (m, 4H), 5.05 (m, 1H),

4.93 (d, J = 8.7 Hz, 1H), 4.20 (d, J = 10.2 Hz, 2H), 4.0-3.67 (m, 7H), 3.15-2.8 (m, 7H), 1.84 (m, 1H), 1.65-1.59 (m, 2H), 0.93 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.36.

Example M8

Phosphonic Acid 8: To a solution of 7 (70 mg, 0.09 mmol) in MeOH (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (49 mg, 90% GS 191478) as a white solid: ^{1}HNMR (CD_3OD) δ 7.83 (dd, 2H), 7.65-7.56 (m, 3H), 7.18 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 7.8 Hz, 2H), 5.59 (d, J = 5.4 Hz, 1H), 4.96 (m, 1H), 4.15 (d, J = 9.9 Hz, 2H), 3.95-3.68 (m, 6H), 3.44 (dd, 2H), 3.16 (m, 2H), 2.99-2.84 (m, 4H), 2.48 (m, 1H), 2.02 (m, 1H), 1.6 (m, 1H), 1.37 (m, 1H), 0.93 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD_3OD) δ 17.45.

Example M9

Sulfonamide 9: A solution of dibenzylphosphonate 6 (0.24 g, 0.31 mmol) in CH_2Cl_2 (0.5 mL) at 0°C was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C. Triethylamine (0.17 mL, 1.20 mmol) was added followed by the treatment of 4-cyanobenzenesulfonyl chloride (61.4 mg, 0.30 mmol). The solution was stirred for 1 h at 0°C and the product was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the sulfonamide 9 (0.20 g, 77%, GS 191717) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.90 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 7.8 Hz, 2H), 7.36 (m, 10H), 7.11 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.2-4.9 (m, 5H), 4.8 (d, 1H), 4.2 (d, J = 9.9 Hz, 2H), 3.99 (m 1H), 3.94 (m, 3H), 3.7 (m, 2H), 3.48 (broad, s, 1H), 3.18-2.78 (m, 7H), 1.87 (m, 1H), 1.66-1.47 (m, 2H), 0.91 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.3.

Example M10

Sulfonamide 10: A solution of dibenzylphosphonate 6 (0.23 g, 0.29 mmol) in CH_2Cl_2 (0.5 mL) at 0°C was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C. Triethylamine (0.16 mL, 1.17 mmol) was added followed by the treatment of 4-trifluoromethyl benzenesulfonyl chloride (72 mg, 0.29 mmol). The solution was stirred for 1 h at 0°C and the product was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the sulfonamide (0.13 g, 50%, GS 191479) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.92 (d, J = 8.1 Hz, 2H), 7.81 (d, J = 8.1 Hz, 2H), 7.36 (m, 10H), 7.12 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.4 Hz, 2H), 5.65 (d, J = 5.1 Hz, 1H), 5.20-4.89 (m, 6H), 4.20 (d, J = 9.9 Hz, 2H), 3.95 (m, 1H), 3.86 (m, 3H), 3.71 (m, 2H), 3.19-2.78 (m, 7H), 1.86 (m, 1H), 1.65 (m, 2H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.3.

Example M11

Phosphonic Acid 11: To a solution of 10 (70 mg, 0.079 mmol) in MeOH (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (50 mg, 90%, GS 191480) as a white solid: ^{1}H NMR (CD_3OD) δ 8.03 (dd, 2H), 7.90 (dd, 2H), 7.17 (d, J = 8.1 Hz, 2H), 6.91 (d, J = 7.8 Hz, 2H), 5.59 (d, J = 5.7 Hz, 1H), 4.94 (m, 1H), 4.15 (d, J = 10.2 Hz, 2H), 3.94-3.72 (m, 6H), 3.48 (m, 1H), 3.2-3.1 (m, 3H), 3.0-2.9 (m, 2H), 2.47 (m, 1H), 2.06 (m, 1H), 1.56 (m, 1H), 1.37 (m, 1H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD_3OD) δ 17.5.

Example M12

Sulfonamide 12: A solution of dibenzylphosphonate 6 (0.23 g, 0.29 mmol) in CH_2Cl_2 (0.5 mL) at 0°C was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30

min at $0^{o}C$ and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C. Triethylamine (0.16 mL, 1.17 mmol) was added followed by the treatment of 4-fluorobenzenesulfonyl chloride (57 mg, 0.29 mmol). The solution was stirred for 1 h at 0°C and the product was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the sulfonamide (0.13 g, 55%, GS 191482) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.81 (m, 2H), 7.38 (m, 10H), 7.24 (m, 2H), 7.12 (d, J = 8.1 Hz, 2H), 6.82 (d, J = 8.4 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.17 (m, 4H), 5.0 (m, 1H), 4.90 (d, 1H), 4.20 (d, J = 9.9 Hz, 2H), 3.97 (m, 1H), 3.86 (m, 3H), 3.73 (m, 2H), 3.6 (broad, s, 1H), 3.13 (m, 1H), 3.03-2.79 (m, 6H), 1.86 (m, 1H), 1.66-1.58 (m, 2H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.3.

Example M13

Phosphonic Acid 13: To a solution of 12 (70 mg, 0.083 mmol) in MeOH (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (49 mg, 90%, GS 191483) as a white solid: ^{1}H NMR (CD_3OD) δ 7.89 (m, 2H), 7.32 (m, 2H), 7.18 (d, J = 8.4 Hz, 2H), 6.9 (d, J = 8.1 Hz, 2H), 5.59 (d, J = 5.1 Hz, 1H), 4.94 (m, 1H), 4.16 (d, J = 9.9 Hz, 2H), 3.94 (m, 1H), 3.85-3.7 (m, 5H), 3.43 (dd, 1H), 3.15-2.87 (m, 5H), 2.48 (m, 1H), 2.03 (m, 1H), 1.59-1.36 (m, 2H), 0.93 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD_3OD) δ 17.5.

Example M14

Sulfonamide 14: A solution of dibenzylphosphonate 6 (0.21 g, 0.26 mmol) in CH_2Cl_2 (0.5 mL) at $0^{o}C$ was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30 min at $0^{o}C$ and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C. Triethylamine (0.15 mL,

1.04 mmol) was added followed by the treatment of 4-trifluoromethoxybenzenesulfonyl chloride (69 mg, 0.26 mmol). The solution was stirred for 1 h at 0°C and the product was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the sulfonamide (0.17 g, 70%, GS 191508) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.84 (d, J = 9 Hz, 2H), 7.36 (m, 12H), 7.12 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.16 (m, 4H), 5.03 (m, 1H), 4.89 (d, 1H), 4.2 (d, J = 9.9 Hz, 2H), 3.97 (m, 1H), 3.85 (m, 3H), 3.7 (m, 2H), 3.59 (broad, s, 1H), 3.18 (m, 1H), 3.1-3.0 (m, 3H), 2.96-2.78 (m, 3H), 1.86 (m, 1H), 1.66-1.5 (m, 2H), 0.93 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{1}P NMR ($CDCl_3$) δ 20.3.

Example M15

Phosphonic Acid 15: To a solution of 14 (70 mg, 0.083 mmol) in MeOH (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (50 mg, 90%, GS 192041) as a white solid: ^{1}H NMR (CD_3OD) δ 7.95 (dd, 2H), 7.49 (dd, 2H), 7.17 (dd, 2H), 6.92 (dd, 2H), 5.58 (d, J = 5.4 Hz, 1H), 4.89 (m, 1H), 4.17 (d, J = 9 Hz, 2H), 3.9 (m, 1H), 3.82-3.7 (m, 5H), 3.44 (m, 1H), 3.19-2.9 (m, 5H), 2.48 (m, 1H), 2.0 (m, 1H), 1.6 (m, 1H), 1.35 (m, 1H), 0.93 (d, J = 6.0 Hz, 3H), 0.88 (d, J = 6.0 Hz, 3H); ^{31}P NMR (CD_3OD) δ 17.4.

Example M16

Sulfonamide 16: A solution of dibenzylphosphonate 6 (0.59 g, 0.76 mmol) in CH_2Cl_2 (2.0 mL) at 0°C was treated with trifluoroacetic acid (1.0 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C. Triethylamine (0.53 mL, 3.80 mmol) was added followed by the treatment of hydrogen chloride salt of 3-pyridinylsulfonyl chloride (0.17 g, 0.80 mmol, prepared according to Karaman, R. *et al. J. Am. Chem. Soc.* 1992, 114, 4889). The solution was stirred for 30 min at 0°C and warmed to room temperature for 30 min. The product was partitioned between CH_2Cl_2 and saturated $NaHCO_3$.